CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761037Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 6, 2017
From: Keith Marin, Senior Regulatory Research Reviewer,WO66, RM 2604, ODE/DAGRID/GDHB

To: Christine Ford, Senior Regulatory Health Program Manager, CDER/OND/ODEII/DPARP

Subject: CDRH Consult, BLA 761037, ICC1600907, DMF (b) (4) Final Review, sarilumab 150 and 200mg in pre-filled syringe

1. Summary and Recommendation

An IR was sent to the sponsor on June 22, 2016 requesting additional hemolytic testing. Based on information reviewed BLA 761037, the sponsor has provided sufficient information to determine that the device is non-hemolytic. No additional information is needed.

2. Purpose of Memo

The Center for Drug Evaluation and Research (CDER) has requested a review from the Center for Devices and Radiological Health (CDRH), regarding BLA 761037. The device constituent of this combination product consists of a pre-filled syringe to deliver sarilumab for the treatment of rheumatoid arthritis (RA).

Reviewer's Note: Additional information was requested on June 22, 2016 regarding hemolysis testing and the sponsor committed that they would provide this information. This consult request is to review the hemolysis testing and determine if it is acceptable.

3. Introduction

Sanofi-aventis has submitted an original Biologic License Application (BLA) for sarilumab (SAR153191/REGN88) solution for subcutaneous injection with the proposed proprietary name (b) (4) proposed to be available in 150 mg/1.14 mL and 200 mg/1.14 mL pre-filled syringes. The pre-filled syringes are to be packaged in cartons containing two (2) pre-filled syringe(s) for the 150 mg and 200 mg doses. (b) (4) Sanofi-aventis has submitted the results of the indirect method (extracts) of hemolysis test per ASTM F 756 "Standard Practice for Assessment of Hemolytic Properties of Materials" on the sarilumab PFS fluid path components.

Product	Indication for Use
(b) (4) (sarilumab injection)	(b) (4) indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Reviewer's Note: The sponsor has included drug preparation or patient instructions for use.

4. Documents

Documentation for the device constituent was obtained from BLA 761037 (eCTD location 3.2.P.2, 3.2.P.7, 3.2.R.5 and 3.2.R.6) and DMF (b) (4) Also reviewed were the package labeling and medication guide.

5. Device Description

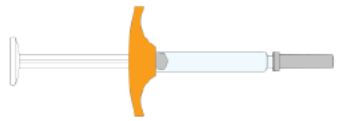
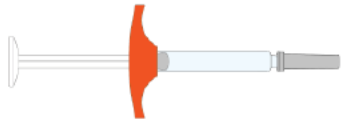
Information on the sarilumab pre-filled syringe was obtained from BLA 761037, eCTD Section 3.2.P.7.

The container closure system for sarilumab solution for injection is composed of the bulk prefilled syringe assembled with a plunger rod required to allow delivery of the PFS content and a finger flange to facilitate PFS grasping and handling. The primary container closure system for sarilumab solution for injection in bulk PFS consists of two packaging components:

- a 1 mL long clear glass syringe barrel equipped with a 27 Gauge (G) ½" (inch) (b) (4) staked needle, protected by a soft elastomeric needle shield,
- an elastomeric ((b) (4) Gray) plunger stopper (b) (4)
- A plunger rod inserted into the plunger stopper to allow delivery of the syringe contents
- A finger flange attached to the syringe flange to facilitate the grasping and handling of the PFS by users.

The 1 mL glass syringe and the plunger stopper are in direct contact with the drug product and are therefore considered as primary packaging components. The plunger rod and the finger flange are considered as secondary packaging components because they are not in direct contact with the drug product and are only in contact with the plunger stopper and the syringe flange.

Table 1 - Illustration of the container closure system for sarilumab 131.6 (=150 mg) and 175 mg/mL (=200 mg)

131.6 mg/mL (=150 mg)	
175 mg/mL (=200 mg)	

The pre-filled syringe components are as follows:

Table 2 - PFS packaging components

Plunger rod	Finger flange	Plunger stopper	Syringe barrel + staked needle + soft needle shield
			

Biocompatibility

In the initial submission, the sponsor provided the chemical characterization, cytoxocity, irritation, sensitization, and acute systemic toxicity.

Table 4 - Correspondence between the biocompatibility tests, concerned components and the supplier protocol and reports references

Biocompatibility tests	Component	Project supplier reference for protocols and reports
Chemical characterization (extractable organic substances)	Glass barrel and needle	(b) (4)
	Soft needle shield	
Cytotoxicity	Glass barrel and needle	
	Soft needle shield	
Irritation	Glass barrel and needle	
Delayed type hypersensitivity (skin sensitization)	Glass barrel and needle	
Acute systemic toxicity	Glass barrel and needle	

*Reviewer's note **(Adequate):** We sent the following comment to the sponsor in request of the hemolysis testing: "You state that the device is in the category of external communicating device with limited (≤24h) contact to tissue, bone or dentin. The device will be administering the drug to the subcutaneous tissue where it is intended to be delivered systemically, and therefore, extractables and leachables can have contact with the blood. We recommend that hemolysis testing is performed on the fluid path components of the final finished device. Accordingly, provide results of hemolysis testing on the needle. Alternatively, provide a justification for why hemolysis testing is not necessary, including information that demonstrates the device materials and any impurities or residuals introduced in the manufacturing process will not result in hemolysis." Sanofi responded by stating to refer to hemolysis test report [QUA-(b) (4) 2016-33507], provided as an attachment to this document.The test report addresses the selection of tested components, the sampling, the conclusion on the hemolysis tests and also the subcontracted (b) (4) laboratory test report. The indirect method (extracts) of hemolysis test per ASTM F 756 was conducted as recommended by the FDA Guidance for devices with indirect contact with circulating blood. This test was performed on the fluid path components (glass syringe with staked needle) of ready for use syringes as supplied to the Sponsor's facility for filling of sarilumab drug product. The hemolysis test report provides evidence that the sarilumab PFS fluid path components are within the non-hemolytic range of 0-2 according to the hemolytic index. Review of the testing protocol show the device is not hemolytic. No additional information is needed.*

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -A Digitally signed by Keith G. Marin -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2017.02.06 16:02:24 -05'00'

Branch Chief Sign-Off	Alan M. Stevens -S	Alan M. Stevens -S 2017.02.07 10:48:46 -05'00'

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/s/

CHRISTINE H FORD
05/19/2017

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 761037
Product Name: Sarilumab

PMR/PMC Description: Conduct a study to assess the pharmacokinetic and pharmacodynamics (PK/PD) parameters and dosing of sarilumab in children ages ≥2 years to 17 years with polyarticular juvenile idiopathic arthritis (pJIA)

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	February 2016 (completed)
	Study/Trial Completion:	September 2017
	Final Report Submission:	March 2018
	Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Given the pediatric patient population, it is appropriate to assess the PK of sarilumab in pediatric patients after the efficacy and safety of sarilumab has been established in adult patients has with RA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of study DRI3925 is to assess the PK profile of sarilumab in patients with pJIA in order to identify the dose (b) (4) in this population. (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A (b) (4) dose study in patients (b) (4)
who are 2 to 17 years of age. (b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 761037
Product Name: Sarilumab

PMR/PMC Description: Conduct a study to assess the efficacy and safety of sarilumab in children ages ≥ 2 years to 17 years with polyarticular JIA

PMR/PMC Schedule Milestones:

Final Protocol Submission:	April 2018
Study/Trial Completion:	June 2022
Final Report Submission:	January 2023
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

Given the patient population, it is appropriate to assess the efficacy and safety of sarilumab in pediatric patients after the efficacy and safety of sarilumab has been established in adult patients has with RA.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

This study fulfills PREA. The goal of study EFC11783 is to evaluate the efficacy and safety of sarilumab in patients with pJIA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☒ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
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- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

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Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

EFC11783 is a (b) (4) study (b) (4) (b) (4) in patients (b) (4) who are 2 to 17 years of age.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials

☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SALLY M SEYMOUR
05/18/2017

LABEL AND LABELING REVIEW AMENDMENT

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 15, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761037
Product Name and Strength:	Kevzara (sarilumab) Injection 150 mg/1.14 mL and 200 mg /1.14 mL
Applicant/Sponsor Name:	Sanofi
Submission Date:	March 22, 2017 and April 24, 2017
OSE RCM #:	2015-2746-1 and 2016-628-1
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD
OMEPRM Acting Deputy Director:	Lubna Merchant, MS, PharmD

1. **REASON FOR AMENDMENT:**

FDA recently issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

2. **COMMENTS TO THE APPLICANT:**

FDA issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 4, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761037
Product Name and Strength:	Kevzara (sarilumab) Injection 150 mg/1.14 mL and 200 mg /1.14 mL
Applicant/Sponsor Name:	Sanofi
Submission Date:	March 22, 2017 and April 24, 2017
OSE RCM #:	2015-2746-1 and 2016-628-1
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the Prescribing Information, carton labeling, and container labels for Kevzara (Appendix A) to determine if it is acceptable from a medication error perspective. BLA 761037 received a complete response on October 28, 2016 due to facility inspection deficiencies. Sanofi submitted a response to the complete response on March 22, 2017. The March 22, 2017 resubmission contained the Prescribing Information, container labeling and container labels. DMEPA previously reviewed the proposed labels and labeling[a] on September 2, 2016.

2 CONCLUSION

The labels and labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] McMillan T. Label and Labeling Review for Kevzara (BLA 761037). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 2. RCM No.: 2015-2746 and 2016-628.

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/s/

TERESA S MCMILLAN
05/15/2017

SARAH K VEE
05/15/2017

LUBNA A MERCHANT
05/15/2017

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING REVIEW MEMO

Date:	May 8, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Gerald Feldman, PhD OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761037
Product:	Kevzara (sarilumab)
Applicant:	Sanofi-aventis U.S. LLC
Submission Date(s):	March 22, 2017 and April 24, 2017

I) RECOMMENDATION

The container labels and carton labeling for Kevzara (sarilumab) Injection, 150 mg/1.14 mL and 200 mg/1.14 mL single-dose pre-filled syringes submitted on April 24, 2017 are acceptable from a quality perspective. However, we recommend the following for section 3 (Dosage Forms and Strengths) of the Full Prescribing Information submitted on March 22, 2017:

1. Remove the parenthetical mg strength per mL as this information does not appear useful because the administration instructions emphasize the entire contents should be administered. Thus, we recommend the strength per mL enclosed by parentheses be removed to be consistent with the labeling of similar biological products packaged in a single-dose pre-filled syringe for subcutaneous administration with a volume greater than 1 mL and to reduce unnecessary information from the prescribing information as follows:

3 DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/1.14 mL [redacted (b) (4)] or 200 mg/1.14 mL [redacted (b) (4)] colorless to pale-yellow solution in a single-dose pre-filled syringe.

II) BACKGROUND AND DISCUSSION

The Applicant submitted BLA 761037 for Kevzara (sarilumab) on October 30, 2015 and received a complete response letter on October 28, 2016. Sanofi-aventis submitted a response to the complete response on March 22, 2017. We previously reviewed the proposed labels and

labeling on October 25, 2017 and found the container labels acceptable.[1] However, our previous review noted concern about the Applicant's proposed inclusion of the strength per mL on the primary display panel of the carton labeling, which upon further discussion with the Division of Medication Error Prevention and Analysis (DMEPA) were determined to be acceptable.

We note that Section 3 (Dosage Forms and Strengths) of the full prescribing information submitted on March 22, 2017 (b) (4)

Thus, we recommend (b) (4)

III) CONCLUSION

The container labels and carton labeling for Kevzara (sarilumab) Injection, 150 mg/1.14 mL and 200 mg/1.14 mL single-dose pre-filled syringes submitted on April 24, 2017 are acceptable from a quality perspective.

We recommend Section 3 (Dosage Forms and Strengths) of the prescribing information be revised (b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[1] Abdus-Samad J. STN 761037 Kevzara (sarilumab) Label and Labeling review. Silver Spring (MD): FDA, CDER, OPQ, OBP (US); 2016 Oct 25.

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/s/

BRENDA V BORDERS-HEMPHILL
05/08/2017

GERALD M FELDMAN
05/08/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 4, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761037
Product Name and Strength:	Kevzara (sarilumab) Injection 150 mg/1.14 mL and 200 mg /1.14 mL
Applicant/Sponsor Name:	Sanofi
Submission Date:	March 22, 2017 and April 24, 2017
OSE RCM #:	2015-2746-1 and 2016-628-1
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the Prescribing Information, carton labeling, and container labels for Kevzara (Appendix A) to determine if it is acceptable from a medication error perspective. BLA 761037 received a complete response on October 28, 2016 due to facility inspection deficiencies. Sanofi submitted a response to the complete response on March 22, 2017. The March 22, 2017 resubmission contained the Prescribing Information, container labeling and container labels. DMEPA previously reviewed the proposed labels and labeling[a] on September 2, 2016.

2 CONCLUSION

The labels and labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] McMillan T. Label and Labeling Review for Kevzara (BLA 761037). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 2. RCM No.: 2015-2746 and 2016-628.

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/s/

TERESA S MCMILLAN
05/04/2017

SARAH K VEE
05/04/2017

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date:	October 25, 2016
Reviewer:	Jibril Abdus-Samad, PharmD Office of Biotechnology Products (OBP)
Through:	Michele Dougherty, PhD, Acting Review Chief OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761037/0
Product:	Kevzara (sarilumab)
Applicant:	Sanofi-aventis U.S. LLC
Submission Dates:	October 30, 2015; March 16; June 14; September 21, October 17, 2016

Executive Summary:

The Applicant addressed the identified deficiencies on the container labels and carton labeling for Kevzara (sarilumab). However, the Applicant's proposed inclusion of the strength per mL on the carton labeling appears potentially confusing and does not appear useful for this product. OBP and the Division of Medication Error Prevention and Analysis (DMEPA) will meet to discuss this issue further. Considering this BLA will receive a CR, I will reserve comment on the acceptability of the container labels and carton labeling until the application is otherwise adequate.

Background and Summary Description:

The Applicant submitted BLA 761037/0 Kevzara (sarilumab) on October 30, 2015 which included proposed container labels and carton labeling. Subsequent to the Applicant's withdrawal of the initially proposed proprietary name, (b) (4) to Kevzara, the Applicant submitted revised container labels and carton labeling on March 16, 2016. On June 14, 2016, the Applicant submitted updated carton labeling due to changes in background color and location of text. Therefore, this review evaluates the March 16, 2016 container labels and the June 14, 2016 carton labeling. The Applicant in Table 1 lists the proposed characteristics of Kevzara (sarilumab).

Table 1: Proposed Product Characteristics of Kevzara (sarilumab).

Proprietary Name:	Kevzara
Proper Name:	sarilumab
Indication:	interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs
Dose:	• 200 mg once every 2 weeks • 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes
Route of Administration:	Subcutaneous injection
Dosage Form:	Injection
Strength and Container-Closure:	150 mg/1.14 mL, 200 mg/1.14 mL prefilled syringes (PFS)
Storage and Handling:	Refrigerate at 36◦F to 46◦F (2◦C to 8◦C) in original carton to protect from light. Do not freeze. Do not shake. Use syringe within 14 days after taking out to the refrigerator[1].

Materials Reviewed:

Container Labels

\\cdsesub1\evsprod\bla761037\0011\m1\us\container-150mg-pfsyringe.pdf

\\cdsesub1\evsprod\bla761037\0011\m1\us\container-200mg-pfsyringe.pdf

Carton Labeling

\\cdsesub1\evsprod\bla761037\0023\m1\us\carton-150mg-2ct-pfsyringe.pdf

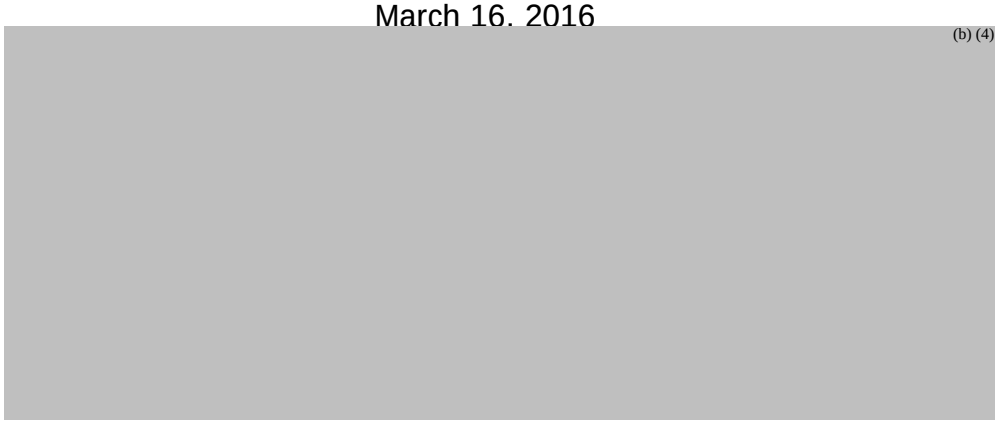
\\cdsesub1\evsprod\bla761037\0023\m1\us\carton-200mg-2ct-pfsyringe.pdf

[1] The Applicant placed this storage information in the Instructions for Use only.

Start of Sponsor Material

Container Labels
March 16, 2016

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *not applicable. The container label is a partial label; however there may be space to add some additional information*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *conforms*.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; *conforms*.

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

Start of Sponsor Material

Carton Labeling
Submitted June 14, 2016

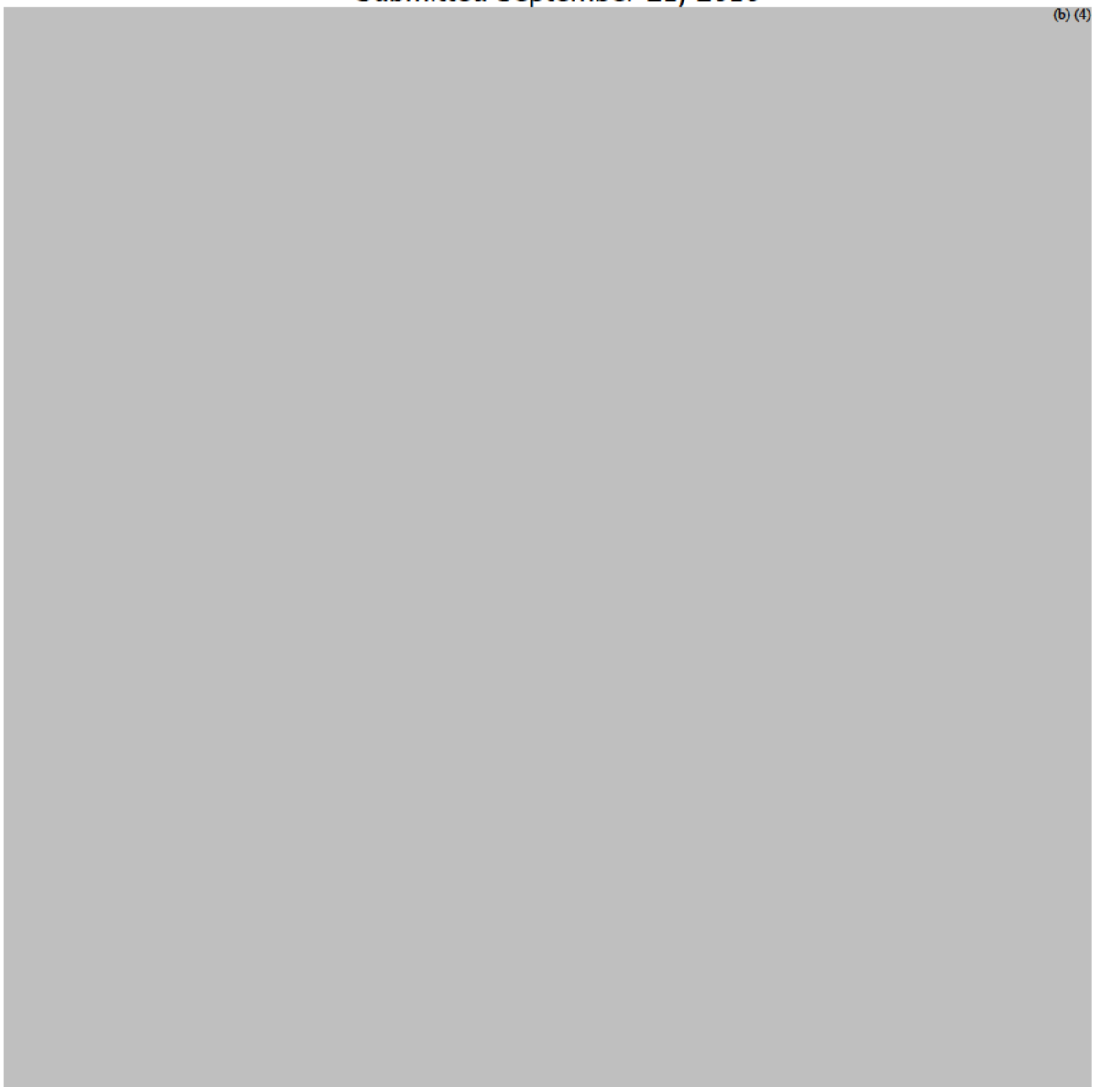
(b) (4)

Carton Labeling
Submitted June 14, 2016

(b) (4)

Carton Labeling
Submitted September 21, 2016

(b) (4)



Carton Labeling
Submitted October 17, 2016

(b) (4)

End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*.

b) The name, addresses, and license number of manufacturer; *conforms*.

c) The lot number or other lot identification; *conforms*.

d) The expiration date; *conforms*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative”; *conforms*.

f) The number of containers, if more than one; *conforms*.

> The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *does not conform*.
> *See discussion below regarding “Strength Presentation*.”

g) The recommended storage temperature; *does not conform*.
There is no information on the carton labeling regarding storage outside the refrigerator, which appears in the instructions for use (IFU).

> OBP Request: We note the room temperature storage instructions appear in the instructions for use (IFU). However, the carton labeling lacks this information. Additionally, there is no method for end-users to track when they removed the product from refrigerator storage. Therefore, revise the storage instructions to include room temperature storage instructions that appear in the IFU, do not shake, and to store in the carton to protect from light.

Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do NOT freeze. Do NOT shake.
If needed, patients/caregivers may store KEVZARA at room temperature up to 77°F (25°C) up to 14 days in the outer carton. Do not store above 77°F (25°C). After removal from the refrigerator, use KEVZARA within 14 days or discard.
Date removed from the refrigerator ___/___/___.
Applicant revised as requested.

h) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *does not conform*. *See comment above to add "Do NOT shake." Applicant revised as requested*.

i) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

j) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

k) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

l) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

m) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

n) The adjuvant, if present; *not applicable*.

o) The source of the product when a factor in safe administration; *not applicable*.

p) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

q) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency”; *conforms*.

r) The statement “Rx only” for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR 601.2(a)]. *Kezvara (sarilumab) is a monoclonal antibody, therefore exempt*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *conforms*.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms. We recommend reformatting the statement of ingredients. See 21 CFR 201.100 below.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform*. *See discussion below regarding "Strength Presentation."*

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; *does not conform*.

OBP Request: Revise the list of ingredients to state the volume delivered and the milligram amounts of each ingredient. For example:

> Each prefilled syringe delivers 1.14 mL of solution containing 150 mg sarilumab, arginine (8.94 mg), histidine (3.71 mg), polysorbate 20 (2.28 mg), sucrose (57 mg) and Water for Injection, USP.
> *Applicant revised as requested*.

Strength Presentation

The initially proposed prominent strength presentation (150 mg and 200 mg) on the carton labeling did not include the volume (150 mg/1.14 mL and 200 mg/1.14 mL). OBP and DMEPA requested the Applicant revise the carton labeling accordingly. The Applicant revised the carton labeling as instructed, however, they also included the strength per mL (131.6 mg/mL and 175.4 mg/1.14 mL). Of note, the Applicant did not propose the strength per mL in the PI.

USP Generals Chapters <7>: Labeling recommends the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength/mL enclosed by parentheses. Typically in PFS (b) (4) for subcutaneous use, the volumes are usually 1 mL or less (the strength per mL is omitted). Therefore, this scenario with Kevzara appears uncommon.

For Kevzara, I find the inclusion of the strength per mL does not appear useful because the administration instructions in the PI and IFU emphasize the entire contents should be administered. Furthermore, the Kevzara product has unusual total deliverable volume (1.14 mL) and strength per mL (131.6 mg/mL and 175.4 mg/mL). Considering patients are usually the end-users for this product, inclusion of strength per mL may be confusing. If this product was (1) designed

with a PFS with graduations or markings to administer partial contents for certain doses or (2) packaged in a vial for intravenous admixture, then it seems more appropriate to provide the strength per mL in the labels and labeling.

During initial discussions, DMEPA concurred with the Applicant's proposal to add the strength per mL on the carton labeling for consistency with USP General Chapters <7>: Labeling. OBP and DMEPA will meet to discuss this issue further. Considering this BLA will receive a CR, I will reserve comment on the acceptability of the container labels and carton labeling until the application is otherwise adequate.

Conclusions:

The Applicant addressed the identified deficiencies on the container label and carton labeling for Kevzara (sarilumab). However, the Applicant's proposed inclusion of the strength per mL on the carton labeling appears potentially confusing and does not appear useful for this product. OBP and DMEPA will meet to discuss this issue further. Considering this BLA will receive a CR, I will reserve comment on the acceptability of the container labels and carton labeling until the application is otherwise adequate.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIBRIL ABDUS-SAMAD
10/25/2016

MICHELE K DOUGHERTY
10/25/2016

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761037

Application Type: Original BLA

Name of Drug: (b) (4) (sarilumab) injection, for subcutaneous use,

Applicant: Sanofi

Receipt Date: October 30, 2015

Goal Date: October 30, 2016

1. Regulatory History and Applicant's Main Proposals

sanofi submitted an original Biologic Licensing Application for sarilumab, a human IgG1 monoclonal antibody for use in treatment of patients with rheumatoid arthritis (RA). The PI also includes a Medication Guide and Instructions for Use.

Carton and container labeling are also included in the submission.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI) dated October 30, 2015. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by February 2, 2016. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

NO 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.
Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

NO 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

(insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch."

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

CHRISTINE H FORD
09/30/2016

SANDRA L BARNES
10/05/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: July 28, 2016
From: Keith Marin, Senior Regulatory Research Reviewer,WO66, RM 2604, ODE/DAGRID/GDHB

To: Christine Ford, Senior Regulatory Health Program Manager, CDER/OND/ODEII/DPARP

Subject: CDRH Consult, BLA 761037, ICC1600093, DMF (b) (4) Final Review, sarilumab 150 and 200mg in pre-filled syringe

1. Summary and Recommendation

Based on information reviewed BLA 761037, the sponsor has provided sufficient information related to the bench performance testing, biocompatibility, sterility, shelf life, and shipping studies to support the safe and effective use of the device. As a result, CDRH/ODE recommends approval for the BLA for this combination product.

The sponsor has identified the following design and release specifications:

Design Specification:

Syringe glass barrel dimensions	(b) (4)
Syringe with needle length	
Seal integrity	
Needle shield removal force	
Break loose	
Gliding force	
Separation force	
Dead space	
Piston seal	
Tightness	No leakage
Dimensional compatibility	(b) (4)
Biocompatibility	Device is biocompatible
Deliverable volume	(b) (4) .14mL

Lot release Specifications:

Test	Analytical Method	Sarilumab PFS Acceptance Criteria		
		Release testing performed on Bulk PFS	Release testing performed on the PFS	End of Shelf-Life (Testing Performed on PFS)
Sterility of bulk Prefilled Syringe	(b) (4)			
Particulate Matter (Light Obscuration)				
Expellable Volume				
Break Loose (BL) and Glide Force (GF)				
Appearance of prefilled syringe a. Verification of plunger rod and finger flange b. Color of plunger rod and finger flange	Visual inspection			
Container Closure Integrity	(b) (4)			
Needle Shield Removal Force	Force measurement			

We recommend that the CDER review division confirm that these performance specifications are adequately valid for the patients and medication being delivered.

2. Purpose of Memo

The Center for Drug Evaluation and Research (CDER) has requested a review from the Center for Devices and Radiological Health (CDRH), regarding BLA 761037. The device constituent of this combination product consists of a pre-filled syringe to deliver sarilumab for the treatment of rheumatoid arthritis (RA).

Reviewer's Note: The sponsor has stated that (b) (4)

3. Introduction

Sanofi-aventis has submitted an original Biologic License Application (BLA) for sarilumab (SAR153191/REGN88) solution for subcutaneous injection with the proposed proprietary name (b) (4) proposed to be available in 150 mg/1.14 mL and 200 mg/1.14 mL pre-filled syringes. The pre-filled syringes are to be packaged in cartons containing two (2) pre-filled syringe(s) for the 150 mg and 200 mg doses. (b) (4)

Product	Indication for Use

(b) (4) (sarilumab injection)	(b) (4) indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Reviewer's Note: The sponsor has included drug preparation or patient instructions for use.

4. Documents

Documentation for the device constituent was obtained from BLA 761037 (eCTD location 3.2.P.2, 3.2.P.7, 3.2.R.5 and 3.2.R.6) and DMF (b) (4). Also reviewed were the package labeling and medication guide.

5. Device Description

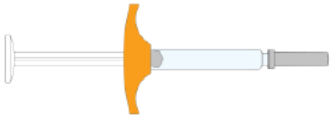
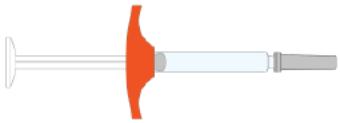
Information on the sarilumab pre-filled syringe was obtained from BLA 761037, eCTD Section 3.2.P.7.

The container closure system for sarilumab solution for injection is composed of the bulk prefilled syringe assembled with a plunger rod required to allow delivery of the PFS content and a finger flange to facilitate PFS grasping and handling. The primary container closure system for sarilumab solution for injection in bulk PFS consists of two packaging components:

- a 1 mL long clear glass syringe barrel equipped with a 27 Gauge (G) ½" (inch) (b) (4) staked needle, protected by a soft elastomeric needle shield,
- an elastomeric ((b) (4) Gray) plunger stopper (b) (4)
- A plunger rod inserted into the plunger stopper to allow delivery of the syringe contents
- A finger flange attached to the syringe flange to facilitate the grasping and handling of the PFS by users.

The 1 mL glass syringe and the plunger stopper are in direct contact with the drug product and are therefore considered as primary packaging components. The plunger rod and the finger flange are considered as secondary packaging components because they are not in direct contact with the drug product and are only in contact with the plunger stopper and the syringe flange.

Table 1 - Illustration of the container closure system for sarilumab 131.6 (=150 mg) and 175 mg/mL (=200 mg)

131.6 mg/mL (=150 mg)	
175 mg/mL (=200 mg)	

The pre-filled syringe components are as follows:

Table 2 - PFS packaging components

Plunger rod	Finger flange	Plunger stopper	Syringe barrel + staked needle + soft needle shield
			

Components

Plunger Rod:

Table 3 - Plunger rod information for sarilumab 131.6 and 175 mg/mL

Material / Type	Color	Supplier of plunger rod
(b) (4)	White	(b) (4)

(b) (4)

Finger Flange:

Table 5 - Plunger rod information for sarilumab 131.6 and 175 mg/mL

Drug product	Material / Type	Color	Supplier of finger flange
Sarilumab 131.6 mg/mL	(b) (4)	Light orange	(b) (4)
Sarilumab 175 mg/mL		Dark orange	

(b) (4)

Glass Syringe:

Table 1 - Composition of the packaging components

Components part	Material / Type	Color	Supplier of syringe with staked needle and soft needle shield
Syringe (1 mL long)	(b) (4) type I, 1 mL long clear glass (b) (4)	Clear	(b) (4)
Staked needle[a]	27G ½ (b) (4)	Steel	
Soft needle shield	(b) (4)	Grey	

a The needle is staked to the syringe barrel (b) (4)
b (b) (4)

(b) (4)

Plunger stopper:

Table 3 - Composition of the plunger stopper

Component	Material / Type	Color	Supplier of plunger stopper
Plunger stopper	(b) (4)	Grey	(b) (4)

Referenced DMF for pre-filled syringe

The primary packaging components in direct contact with the product are subject of Drug Master File (DMF) by the suppliers. Supplier names and DMF references are listed below:

Table 3 - Name and DMF supplier for prefilled syringe primary packaging components

Primary packaging component	Plunger stopper	Syringe barrel (1 mL) with staked needle + soft needle shield
Illustration of primary packaging component		
Supplier name	(b) (4)	
DMF reference number		

Reviewer's Note: The sponsor has referenced DMF (b) (4) for the syringe and provided functional testing for the syringe in the BLA. DMF (b) (4), DMF (b) (4) and DMF (b) (4) have been referenced for the plunger stopper. As this component is in direct contact with the drug, I will defer review of this component to CDER. However, the dimensional compatibility of the syringe barrel and plunger stopper will be assessed within this review. The sponsor has stated in an IR response from April 20, 2016 that functional testing for the pre-filled syringe can be found in 3.2.P.2.3 that they deigned as "essential design outputs". This includes soft needle shield removal force, break loose and glide force testing, and delivery volume.

6. Device Functional Testing

The sponsor states that the functional performance tests were performed by sanofi or by a subcontractor lab in the frame of Design Control management. The key PFS performance tests were identified as part of the "Essential Design Outputs" to ensure the usability of the PFS which is considered as the combination product. It is the sponsor's opinion that three tests performed on measuring equipment, allow physical evaluation of the combination product close to its intended use by the final users:

- SNS pull out force
- Break loose and gliding forces
- Delivery volume

Seal Integrity Testing (Dye Immersion Test)
Protocol: (b) (4)

Acceptance criteria: (b) (4)

Soft Needle Shield Removal Force
Protocol: (b) (4)

Acceptance criteria (b) (4)

Break Loose
Protocol: (b) (4)

Acceptance Criteria: Indicative value for PFS: (b) (4)

Reviewer's Note: It was noted that the testing for break loose consisted of using water filled syringes. Discussion with Mishale Mistry on the HF study brought up that 1 user had difficulty depressing the plunger due to the hand size being too small and how far needed to reach with thumb and another patient had trouble depressing plunger due to grip (had to use other thumb). The study consisted of 30 patients, 31 caregivers, and 15 nurses. Based on this information, I am not too concerned that water was used in the breakloose testing. Furthermore, the sponsor has specified break loose in the lot release specifications.

Separation Force (needle pull out force)
Protocol: (b) (4)

Acceptance Criteria: (b) (4)

Stress Cracking
Protocol: (b) (4)

Acceptance Criteria: None specified

Dead Space
Protocol: (b) (4)

Acceptance Criteria: (b) (4)

Piston seal blowback
Protocol: (b) (4)

Acceptance Criteria: (b) (4)

Tightness test
Protocol: (b) (4)

Acceptance Criteria: (b) (4)

Table 3 - Functional performance results

Test	Sampling	Specifications	Result	Conclusion
Seal Integrity (Dye immersion Test)	50 syringes	(b) (4)	No methylene blue observed	Complies
Break force and Glide Force (with water)	50 syringes		Break Force (N): Min: 1.93, Max: 4.68, SD: 0.53 Glide Force (N): Min: 0.58, Max: 1.97 ; SD : 0.23	Complies
Separation Force (Needle pull out force)	50 syringes		Min: 121.33 N Max: 126.07 N SD: 1.16	Complies
Stress cracking (burst test)	75 syringes		Min: 122.4 bar Max: 200.6 bar	There are no specifications for this test
Dead space (Dead Volume)	50 syringes		Min: 2.8 µL Max 8.5 µL	Complies
Tip cap removal force (NS pull out force)	50 syringes		Min: 8.41N Max: 15.14 N	Complies
Piston seal blowback (Leak test)	50 syringes		No leakage observed	Complies
Piston seal blowback (Tightness test)	50 syringes		No leakage observed	Complies

Reviewer's Note: The sponsor has provided the functional performance testing for the pre-filled syringe. The sponsor has tested according to ISO 7886 and ISO 594 and based on the testing, the device meets the acceptance criteria specified.

Dimensional Compatibility of the plunger rod and plunger

The dimensional compatibility of the plunger rod and plunger stopper assembly is characterized through a functional test using a bulk PFS filled with water, stoppered and assembled with the plunger rod. This test confirms that these two device constituent parts stay assembled when the plunger rod is slowly pulled out.

Table 4 - List of controls performed on plunger rod

Type of controls	Defect/Test	Method	Acceptance criteria
Visual control	Appearance Color	Visual	Complies with AQL defined in internal procedure
Dimensional	Top diameter Body diameter Total length	Measurement	Complies with AQL defined in internal procedure
Functional	Plunger rod screwing	Visual	Complies with AQL defined in internal procedure
Supplier certificate of analysis	Product code, manufacturing and/or expiry date, batch status	Not applicable	Complies with internal procedure

AQL: Acceptance Quality Limit

Batch functional testing

Table 4 - Tested batches characteristics

	Sarilumab 131.6 mg/mL			Sarilumab 175 mg/mL		
Sanofi Winthrop Industrie Batch number	980921	980922	980923	980924	980925	980926
Bulk PFS Regeneron batch number	8090900014	8090900015	8090900016	8090700026	8090700027	8090700028
PFS Regeneron batch number	8141400006	8141400007	8141400008	8141200006	8141200007	8141200008
Manufacturing place	Sanofi Winthrop Industrie, Le Trait					
Filling starting date	(b) (4)					
Packing date						

Table 5 - PFS SNS removal force test results for 131.6 and 175 mg/mL

Test	Procedure	Sampling	Specification	Batch	Results			Test status
					Mean (N)	Min (N)	Max (N)	
SNS removal force	P.5.2.Analytical procedure-LTR-PFS-SNS removal force QUA (b) (4) 2015-12851	Simple sampling plan with control level I according to ISO2859-1 (b) (4)	(b) (4)	980921	10.650	6.023	15.435	Compliant
				980922	10.790	6.448	14.712	Compliant
				980923	10.731	6.507	14.668	Compliant
				980924	10.038	6.899	15.261	Compliant
				980925	9.495	6.572	13.546	Compliant
				980926	10.258	7.074	15.455	Compliant

SNS: Soft Needle Shield

Table 6 - PFS Break loose force test results for 131.6 mg/mL and 175 mg/mL

Test	Procedure	Sampling	Specification	Batch	Results			Test status
					Mean (N)	SD (N)	Mean + k*SD (N)	
Break loose force	P.5.2.Analytical procedure-LTR-Bulk PFS-Break Loose & Glide Force QUA (b) 2015-12166	General sampling plan with control level III according to ISO3951-1 (b) (4)	(b) (4)	980921	7.057	1.129	9.350	Compliant
				980922	6.917	1.041	9.031	Compliant
				980923	6.738	1.104	8.980	Compliant
				980924	7.318	0.982	9.312	Compliant
				980925	7.150	1.007	9.195	Compliant
				980926	7.437	1.022	9.513	Compliant

Table 8 - PFS Delivery volume test results for 131.6 mg/mL and 175 mg/mL

Test	Procedure	Sampling	Specification	Batch	Results			Test status
					Mean (mL)	Min (mL)	Max (mL)	
Delivery volume	P.5.2.Analytical procedure-LTR-Bulk PFS-Volume in container QUA-(b) 2015-12220	Simple sampling plan with control level I according to ISO2859-1 (b) (4)	(b) (4)	980921	1.2440	1.2230	1.2587	Compliant[a]
				980922	1.2381	1.2203	1.2491	Compliant
				980923	1.2398	1.1974	1.2510	Compliant
				980924	1.2422	1.2218	1.2539	Compliant[a]
				980925	1.2397	1.2155	1.2561	Compliant[a]
				980926	1.2380	1.2113	1.2626	Compliant[a]

a During the delivery volume test of batches 980921, 980924, 980925 and 980926, some broken finger flanges were noticed. Following investigations, the root cause was determined to be the consequence of an excessive strength applied on the finger flange which resulted in broken finger flange. That excessive strength was linked to the test method. As a corrective action, it was decided to modify the syringe handling to be more representative of the intended use. Following the handling change, it was shown an equivalence regarding the delivery volumes between the two handling methods; these volumes were compliant with the specification. Moreover, no broken finger flange was observed with the updated handling – the one representative of the intended use.

Reviewer's Note: The sponsor makes a note in the batch functional testing for delivery volume that during the testing, finger flanges were broken due to the test method. The sponsor stated that they modified the flanges to make it more appropriate to the intended use. It is not clear to this reviewer how the flanges were changed and whether it was just changed for the testing or changed for the planned combination product. Furthermore, it is not clear how the integrity of the flanges were validated after this change outside of the delivery volume testing. On May 16, 2016, the sponsor was asked to provide clarification. On June 7, 2016, the sponsor clarified (b) (4)

Table 1 - Glass syringe barrel flange control change

(b) (4)

The sponsor concludes (b) (4)

Needle

Since the submission of the BLA 761037, the ISO 11040-4 Glass barrels for injectables and sterilized subassembled syringes ready for filling was upgraded and new general requirements were published. The ISO 11040-4:2015 general requirements on staked needle, the associated tests and acceptance criteria for sarilumab prefilled syringe presentation are given in the below table. Except the needle pull out force which is part of the functional test performance performed by the sponsor, all tests described hereafter are performed by the supplier on the needle batches.

ISO 11040-4 requirements	Test/requirements	Objective	Method	Acceptance criteria
	Needle external diameter	Measurement of the outside diameter of the needle	Supplier internal procedure	(b) (4)
	Needle internal diameter	Measurement of the inside diameter of the membrane	Supplier internal procedure	
Material and dimensions of the needle tubing shall comply with ISO 9626	Maximum deflection	Assess the maximum deflection of the needle	Supplier internal procedure according to ISO 9626 Appendices C	
			(b) (4)	
Actual needle length shall be in accordance with ISO 7864	Needle length	Measurement of the needle length[b]	Supplier internal procedure according to ISO 7864	
	Primary bevel length	Measurement of the primary bevel length	Supplier internal procedure according to ISO 7864	
Bevel, dimensions, and bond between the glass and the needle shall comply with ISO 7864	Secondary bevel length	Measurement of the secondary bevel length	Supplier internal procedure according to ISO 7864	
	Facet angle	Measurement of the facet angle	Supplier internal procedure according to ISO 7864	
			(b) (4)	

ISO 11040-4 requirements	Test/requirements	Objective	Method	Acceptance criteria
(b) (4)				

a Supplier internal acceptance criteria
b Needle length before being attached to the glass barrel.

Reviewer's Note: In the initial review, we were unable to locate the specifications of the needle component of the syringe. The sponsor stated that as ISO 11040-4 was updated, they provided the requested specifications for the needle and that the needle meets the specifications. It was also noted on page 20 of P.2.4 Container Closure System that complaints were noted during the clinical trial conducted 2011-2015. However, we did not see any mention of how these complaints were addressed in the device section 3.2.P.7 or within the human factors report.

Table 1 - Internal mitigation risk controls and usability risk assessment to address the complaints observed on PFS during phase III clinical studies

Category of the complaint	Description of the complaint	Internal mitigation risk controls		Usability risk assessment part of HFS
		Type of control	Defect description	
Bent Needle	The user found the needle to be bent after decaping the soft needle shield	In-coming Visual control	Bent needle (>2°)[a]	Not encountered during HFS
Blunt Needle	Injection considered by the user as painful	In-coming Functional control	See Table 2	Not encountered during HFS
Clogged Needle	After decaping the soft needle shield, product impossible to inject by the user, due to the needle was clogged	In-coming Functional control	See Table 2	Not encountered during HFS
Broken Needle	The user found the needle broken, after decaping the soft needle shield	In-coming Visual control	See Table 2	Not encountered during HFS

HFS: Human Factor Study
a Classified as a major incoming control according to internal AQL

Table 2 - List of critical incoming controls performed on the staked needle of the syringe component of the prefilled syringe

Part of component	Type of controls	Defect description or test to be performed	Method	Acceptance criteria
Needle	Visual control	No needle, broken needle, reversed needle, no bevel	Visual examination	Complies with AQL defined in internal procedure
		Foreign particles on the needle		
		Needle piercing the NS		
		Detached needle		
		Irregular surface of the needle		
		Glue excess on bottom of the barrel		
		Needle not siliconized		
	Functional control	Hooked or blunt point defect[a]	Puncture of a polyethylene film with the needle	Complies with AQL defined in internal procedure
		Clogged needle[a]	Expelling of water by applying pressure on a plunger rod assembled with a water filled syringe closed by a plunger stopper	
		Needle pull out force	Applying a traction force to disassemble the staked needle from the cone of the syringe	

AQL: Acceptance Quality Limit
a Moreover, a 100% In Process Control at supplier site ensures absence of these defects before assembly into the needle shield

The sponsor stated that the defects of the PFS found during clinical studies were not encountered during the Human Factor Studies. The sarilumab prefilled syringe has been found to be reasonably safe and effective for the intended users, uses and use environments. Since the submission of the BLA 761037 for

sarilumab to the agency, the internal SOP on incoming controls for the syringe with the staked needle component was upgraded. The critical incoming controls performed on syringe component of the sarilumab prefilled syringe are found in the below table and the visual control of the broken needle and the functional control of the hooked or blunt point defect were already part of the submitted section 3.2.P.7. I find the sponsor's additional information acceptable.

On July 15, 2016 the following IR was sent to the sponsor to obtain clarification on why the needle breakage problems were occurring in the clinical study:

In your submission dated June 22, 2016 (response to Question #1 in the 6/17/16 information request), related to the complaints noted during the clinical trial conducted 2011-2015, you state "that the defects of the PFS found during clinical studies were not encountered during the Human Factor Studies. The sarilumab prefilled syringe has been found to be reasonably safe and effective for the intended users, uses and use environments. Since the submission of the BLA 761037 for sarilumab to the agency, the internal SOP on incoming controls for the syringe with the staked needle component was upgraded. The critical incoming controls performed on syringe component of the sarilumab prefilled syringe are found in the below table and the visual control of the broken needle and the functional control of the hooked or blunt point defect were already part of the submitted section 3.2.P.7." However, your response does not answer why the needle breakage problems were occurring in the first place during the clinical study, and whether or not a root cause analysis was conducted on the clinical study adverse event reports. Please provide additional information on why the needle breakage was occurring and whether a root cause analysis was conducted to determine why this was occurring.

In the sponsor's response, they stated that there were four complaints of broken needles out of over 111,951 injections. Of the four complaints of broken needles, three were returned for investigation. The fourth syringe was disposed of by the patient and not available for investigation. The investigations concluded that the needle breakage was likely due to the misuse of the syringe by the user during the needle shield removal process (based on visual confirmation that the needle was present and the needle shield analysis that showed correct placement marks of the needle inside the needle shield rubber). This was also supported by no anomalies found during the manufacturing or packaging of these batches. The sponsor states that there is 100% control in place with the syringe supplier that verifies that there are no defects with the needles (no hooked, clogged, or blunt points prior to assembly) and the total length of assembly is validated to ensure there is no dislocation of the needle. The sponsor has provided a table of each of the broken needle complaints and the conclusions of the root cause analysis:

Description of the complaint	Adverse Event	Quality investigation	Technical investigation of the returned sample	Conclusion
Patient stated that the syringe needle top broke off in the abdomen during injection.	Yes [EFC11072 16.2.7 – AE Listing]	The most probable root cause is a handling error according to a documentation root cause analysis exercise which excluded potential root causes related to: equipment, machinery, instruments, technology, media (external environment, surroundings), materials (raw materials, products, consumables) and methods (procedures, measures, manufacturing/operating/inspection processes). Packaging and labeling process: Following review of the quality documentation (batch record, deviations) no issue was observed. No root cause was identified at the packaging site for this defect.	N/A The syringe was disposed of by the patient and not available for investigation.	Based on the root cause analysis, including the quality investigation, there is no evidence that the product is the probable cause for the adverse event and product technical complaint. Therefore, it is likely that the top of the needle broke due to a handling error (manipulation) by the patient.

APPEARS THIS WAY ON ORIGINAL

Description of the complaint	Adverse Event	Quality investigation	Technical investigation of the returned sample	Conclusion
A kit was returned because the syringe needle was broken.	No	Incoming control performed on the components were compliant and all the batches used were released for manufacturing process. Manufacturing process: Following review of the quality documentation (batch record, deviation, Certificate of Conformity), no issue was observed. The rejected defect rates observed during the 100% visual inspection step and also during the 100% check after plunger rod insertion step (including defects related to the complaint such as bent, dislocated or pierced NS) are not atypical regarding the thresholds in place. The defect observed in the complaint cannot be related to the manufacturing process. No root cause was identified at Sanofi, Le Trait manufacturing site for this defect. Packaging and labeling process: Following review of the quality documentation (batch record, deviations) no issue was observed. No root cause was identified at the packaging site for this defect.	Following visual, microscopic and X-ray analysis, the investigation demonstrated: Evidence of the correct manufacturing process at syringe supplier facility: (b) (4) Evidence of syringe manipulation: (b) (4)	Based on the quality and technical investigation at the Sanofi, Le Trait manufacturing site, the most probable root-cause is the needle was broken during the handling of the PFS by final user. The needle shield is flexible and mishandling can occur if the needle-shield is twisted during removal.

Description of the complaint	Adverse Event	Quality investigation	Technical investigation of the returned sample	Conclusion
Treatment kit allocated could not be dispensed to the patient because the needle was broken when they opened the treatment box.	No	Incoming control performed on the components were compliant and all the batches used were released for manufacturing process. The rejected defect rates observed during the 100% visual inspection step and also during the 100% check after plunger rod insertion step (including defects related to the complaint such as bent, dislocated or pierced NS) are not atypical regarding the thresholds in place. The defect observed in the complaint cannot be related to the manufacturing process. No root cause was identified at Sanofi, Le Trait manufacturing site for this defect. Packaging and labeling process: Following review of the quality documentation (batch record, deviations) no issue was observed. No root cause was identified at the packaging site for this defect.	Following visual, microscopic and X-ray analysis, the investigation demonstrated: Evidence of the correct manufacturing process at syringe supplier facility: (b) (4) Evidence of syringe manipulation: (b) (4)	Based on the quality and technical investigation at the Sanofi, Le Trait manufacturing site, the needle was broken and the position of the broken part didn't correspond to its initial position. The needle wasn't broken before removing of the NS. No information regarding a NS deviation was reported even if the investigation highlights an important needle deviation. Based on the X-ray and visual inspection of the syringe it appears that the syringe has been manipulated prior to attempted use and recapped prior to returning. By these observations, the most probable root-cause is an incorrect manipulation of the syringe. The technical investigation performed on the returned sample did not validate the description provided by the complainant (i.e. the needle was broken when the box was opened). Based on the forensic evidence provided in the investigation, the syringe had to be manipulated in order to produce the broken needle. Therefore, it is probable that this occurred but was not described by the complainant on the complaint form.

Description of the complaint	Adverse Event	Quality investigation	Technical investigation of the returned sample	Conclusion
A broken needle was observed.	No	Incoming control performed on the components were compliant and all the batches used were released for manufacturing process. The rejected defect rates observed during the 100% visual inspection step and also during the 100% check after plunger rod insertion step (including defects related to the complaint such as bent, dislocated or pierced NS) are not atypical regarding the thresholds in place. The defect observed in the complaint cannot be related to the manufacturing process. No root cause was identified at Sanofi, Le Trait manufacturing site for this defect. Packaging and labeling process: Following review of the quality documentation (batch record, deviations) no issue was observed. No root cause was identified at the packaging site for this defect.	Following visual, microscopic and X-ray analysis, the investigation demonstrated: Evidence of the correct manufacturing process at syringe supplier facility: (b) (4) Evidences of syringe manipulation: (b) (4)	Based on the quality and technical investigation at the Sanofi, Le Trait manufacturing site, there is no particular event detected during the manufacturing process which could have led to this defect. The needle wasn't broken before removing of the NS by the final user. The needle was certainly broken due to manipulation. Consequently, this event is related to a mishandling issue.

The sponsor came to the conclusion that based on the investigation and the controls in place no additional corrective actions are needed. Based on my review of this information, I would agree with the conclusion as the cases all appear to support breakage related to usage and not manufacturing.

Biocompatibility

The sponsor has stated that all biocompatibility studies were performed by a sub-contractor lab which is in charge of the redaction of protocols, their realization and the redaction of study reports for syringe (glass barrel and needle) and soft needle shield. For the plunger rod and finger flange, it was done by the supplier and that the testing complies with ISO 10993 requirements. The biocompatibility declaration of compliance according to ISO 10993-1 is provided in document referenced QUA-(b) (4)-2015-01748 for syringe (glass barrel and needle) and soft needle shield. The biocompatibility compliance statement from supplier for the plunger rod and finger flange is provided in document referenced QUA-(b) (4)-2015-16693. The reference of the sarilumab PFS components in this document are described below:

- Plunger rod: supplier product code (b) (4)
- Finger flange light orange for 131.6 mg/mL strength: supplier product code (b) (4)
- Finger flange dark orange for 175 mg/mL strength: supplier product code (b) (4)

The sponsor states the following biological risks were evaluated for the pre-filled syringe: cytotoxicity, irritation, hypersensitivity, acute systemic toxicity, and chemical characterization.

Table 4 - Correspondence between the biocompatibility tests, concerned components and the supplier protocol and reports references

Biocompatibility tests	Component	Project supplier reference for protocols and reports
Chemical characterization (extractable organic substances)	Glass barrel and needle	(b) (4)
	Soft needle shield	
Cytotoxicity	Glass barrel and needle	
	Soft needle shield	
Irritation	Glass barrel and needle	
Delayed type hypersensitivity (skin sensitization)	Glass barrel and needle	
Acute systemic toxicity	Glass barrel and needle	

*Reviewer's note **(Adequate):** Reviewing the biocompatibility section, it appears that the sponsor has stated that the biocompatibility declaration of compliance according to ISO 10993-1 is provided in document referenced QUA-(b) (4)-2015-01748 for syringe (glass barrel and needle) and soft needle shield, and that the biocompatibility compliance statement from supplier for the plunger rod and finger flange is provided in document referenced QUA-(b) (4) 2015-16693. However, these documents cannot be located. An IR was sent on May 23, 2016 asking the sponsor to provide the exact location on where the biocompatibility testing can be found. On June 7, 2016, the sponsor provided the location of the full biocompatibility compliance documentation that was referenced in Module P.2.4 Container Closure System PFS in Section 3.4.1 Biocompatibility. Additionally, we asked the sponsor to provide the complete test reports for the (b) (4) components and provide hemolysis and material mediated pyrogenicity testing for the needle. The sponsor provided this information as noted above and Dr. Sarah Mollo assisted in the review of the adequacy of the information. The sponsor has performed the following testing on the syringe and needle:*

- *Cytotoxicity (according to ISO 10993-5)*
- *Irritation (according to ISO 10993-10)*
- *Delayed type hypersensitivity (according to ISO 10993-10)*
- *Acute systemic toxicity (according to ISO 10993-11)*
- *Chemical characterization (according to ISO 10993-18)*

The syringe is pre-filled and therefore, CDER is reviewing the fluid path as it is the primary container closure. I reviewed the biocompatibility information for the surface contacting components of the syringe and needle. The testing for the syringe was adequate. The sponsor did not provide testing to address hemolysis or material-mediated pyrogenicity of the needle. As the needle can be considered part of the fluid-path, the lead-reviewer contacted CDER to ask if CDRH should perform a biocompatibility evaluation of the needle because if so, we would send

IRs regarding the hemolysis and pyrogenicity endpoints (see attached email). CDER stated that they had not reviewed those endpoints, and that the IR should go out as planned. The IR (sent June 17, 2016) asked for the testing or a rationale for why it was not needed. The sponsor provided a rationale for why material-mediated pyrogenicity testing is not necessary based on the materials used. However, for hemolysis testing, the sponsor's rationale stated that the device was tissue contacting and therefore, did not require hemolysis testing. This rationale for not including hemolysis testing is not sufficient, as the needle is in the fluid path, which will have indirect contact with the blood. This was conveyed to the sponsor in a second IR (sent July 1, 2016). The sponsor has responded (b) (4)

Shipping Studies

Simulated shipping validation studies are performed on packed prefilled syringe (PFS) as base unit. Simulated road (truck), air and sea freight shipping studies are performed per ASTM D4169-14, Standard Practice for Performance Testing of Shipping Containers and Systems.

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's note: *The controls performed after the simulation of transport showed that the visual, functional, microbiological tested aspects of PFS as well as the product quality including integrity of the PFS confirm the absence of transport impact. I find the testing acceptable.*

Shelf Life

The sponsor has provided a summary of results from stability studies examining the effects of long-term storage and temperature stress on protein quality, functionality, performance, and container closure integrity of the finished prefilled syringes (PFS).

Table 3: Primary Lot Sarilumab Prefilled Syringe Long-Term Stability Tests and Test Intervals

Test	Long-Term Storage Condition (2°C to 8°C)									
	Test Interval (months)									
	0	1	3	6	9	12	18	24	30	36
Appearance of Solution	X	X	X	X	X	X	X	X	X	X
Color of Solution	X	X	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X	X	X
Total Protein Content (A_{280})	X	X	X	X	X	X	X	X	X	X
Purity by Reduced CE-SDS	X	X	X	X	X	X	X	X	X	X
Purity by Non-Reduced CE-SDS	X	X	X	X	X	X	X	X	X	X
Purity by SE-HPLC	X	X	X	X	X	X	X	X	X	X
Charge Variant Analysis by CEX-HPLC	X	X	X	X	X	X	X	X	X	X
Potency by Bioassay	X	X	X	X	X	X	X	X	X	X
Particulate Matter: light obscuration	X	NR	NR	X	NR	X	X	X	X	X
Particulate Matter: MFI	X	NR	NR	X	NR	X	X	X	X	X
Bacterial Endotoxin Content	X	NR	NR	NR	NR	X	NR	X	NR	X
Break-loose and Glide Forces	X	NR	NR	X	NR	X	X	X	X	X
Sterility of pre-filled syringe	X	NR	NR	NR	NR	X	NR	X	NR	X
Container Closure Integrity	NR	NR	NR	NR	NR	X	NR	X	NR	X
Expellable Volume[a]	NR	NR	NR	NR	NR	X	X	X	NR	X
Needle Shield Removal Force[b]	NR	NR	NR	NR	NR	X	X	X	NR	X

Stability Study Number	RG88-RS0044-06/14									
PFS Lot No. / Date of Assembly	8141200003 / 05Jun2014									
Bulk PFS Lot No. / Date of Fill	8090700023 / 17Mar2014									
Formulation	175 mg/mL in an aqueous (b) (4) solution, pH 6.0, containing 21 mM histidine1, 45 mM arginine , 5% sucrose (w/v), and 0.2% polysorbate 20 (w/v)									
Storage Container	1 mL long clear glass syringe with a staked (b) (4) needle, closed with a (b) (4) elastomer plunger stopper and (b) (4) elastomer needle shield									
Study Initiation Date	02Jul2014	Real Age from Date of Bulk PFS Fill (Months)								
Storage Condition	5°C	3.6	4.6	6.6	9.6	12.6	15.6	21.6	27.6	33.6	39.6
Assay	End-of-Shelf-Life Acceptance Criteria	Stability Protocol Time Point (Months)									
		t=0[a]	1	3	6	9	12	18	24	30	36
Particulate Matter (MFI)	Testing not required Specification in place during clinical development: Report particles/container for information (b) (4)	47419	NR	NR	27662	NR	16902	13051			
Bacterial Endotoxin Content	Testing not required Specification in place during clinical development: (b) (4)	<0.0500	NR	NR	NR	NR	0.0003	NR			
Sterility (filled container)	Meets USP/ Ph. Eur. requirements	Pass	NR	NR	NR	NR	Pass	NR			
Break Loose and Glide Force	a. Break-loose force: ≤ (b) (4) N b. Gliding force: ≤ (b) (4) N	a. 5.91 b. 14.30	NR	NR	a. 6.60 b. 15.68	NR	a. 6.43 b. 16.86	a. 6.92 b. 16.51			
Container Closure Integrity	No dye detected	NR	NR	NR	NR	NR	NDD	NR			
Expellable Volume	(b) (4) mL	NR	NR	NR	NR	NR	1.23	1.23			
Needle Shield Removal Force	(b) (4)	NR	NR	NR	NR	NR	14	16			

The sponsor states that no meaningful changes in glide force were observed for the 131.6 mg/mL concentration at the real age of 24 months. Increases of up to (b) (4) N were seen in glide force for the 175 mg/mL concentration; however, all lots were well within the end-of-shelf life specification after the 18- month protocol time point (22 months from the date of fill of the 175 mg/mL

concentration). They also state that no meaningful changes in break loose were observed for either concentration of the PFS. Testing for expellable volume and needle shield removal force was added to the PFS primary stability protocols commencing with the 12-month time point. No notable changes were observed between the 12-month and 18-month protocol time points and all results were well within end-of shelf life acceptance criteria. Sterility and container closure integrity are monitored to ensure the absence of contamination of the primary container closure. Container closure integrity was maintained at the most recent required protocol time point (12 months) for sarilumab PFS. Sterility and container closure integrity are also performed as part of the Bulk PFS primary stability studies, which examine the source lots used to manufacture the PFS lots monitored in the primary stability studies. All sterility and container closure integrity results passed at the 24-month time point from the date of fill.

The sponsor argues that the long-term stability data provided in Module P.8.3 for the functional testing (break loose/ glide force, expellable volume, and needle shield removal force) performed on the PFS at the real age of 24 and 22 months for the 131.6 mg/mL and 175 mg/mL concentrations, respectively, support the usability of the PFS at the proposed end-of-shelf life of 24 months from the date of fill of the Bulk PFS. In addition, acceptable data from sterility and container closure integrity testing performed on the PFS and Bulk PFS at 12-month and 24-month stability protocol time points, respectively, ensure the absence of contamination of the primary container closure (Bulk PFS) at the proposed end-of-shelf life of 24 months from the date of fill of the Bulk PFS

Reviewer's Note: In review of table 3 of the stability summary, the sponsor states that they have performed stability testing by testing the function of the syringe, specifically break loose/glide force, sterility, container closure integrity, expellable volume, and needle shield removal force. However, the only thing this reviewer was able to locate was the summary table, not the testing to support that the device functions at the end of your stated shelf life. The sponsor was asked on May 23, 2016 to submit the testing performed to support that your device will function at the end of its stated shelf life. The sponsor stated on June 7, 2016, an updated Module P.8.3 Stability Data - PFS document that included the 18-month time point stability data (~24 month time point from the date of fill) was provided as part of a complete stability update to BLA 761037 with the response to the information request. The sponsor provided the necessary shelf life studies to demonstrate device function at end of shelf life.

Lot release Specifications:

Test	Analytical Method	Sarilumab PFS Acceptance Criteria		
		Release testing performed on Bulk PFS	Release testing performed on the PFS	End of Shelf-Life (Testing Performed on PFS)

APPEARS THIS WAY ON ORIGINAL

Sterility of bulk Prefilled Syringe		(b) (4)
Particulate Matter (Light Obscuration)		
Expellable Volume		
Break Loose (BL) and Glide Force (GF)		
Appearance of prefilled syringe a. Verification of plunger rod and finger flange b. Color of plunger rod and finger flange	Visual inspection	(b) (4)
Container Closure Integrity		
Needle Shield Removal Force		

7. CDRH Comments for Review Team

- Please ensure that a separate consult has been sent to CDRH Office of Compliance to assist with any necessary device facilities inspections required for approval of this BLA.
- Biocompatibility was evaluated for the syringe component of the device in terms of contact of the syringe with the patient/provider and needle pathway
- Sterility of the drug device will be deferred to CDER. (b) (4) .

If you have any questions, please contact LCDR Keith Marin at 301-796-2462.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Keith G. Marin -A Digitally signed by Keith G. Marin -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -A, 0.9.2342.19200300.100.1.1=0011250397 Date: 2016.08.17 14:01:28 -04'00'
Branch Chief Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2016.08.18 10:45:03 -04'00'

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE H FORD
10/03/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
BLA# 761037	BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) (later changed to Kevzara) Established/Proper Name: sarilumab Dosage Form: injection, pre-filled syringes Strengths: 150 and 200 mg		
Applicant: sanofi Agent for Applicant (if applicable):		
Date of Application: October 30, 2015 Date of Receipt: October 30, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 10/30/2016	Action Goal Date (if different): 10/28/2016 (Friday)	
Filing Date: 12/19/15	Date of Filing Meeting: 12/17/15	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): rheumatoid arthritis (RA)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☒ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☒ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 100632	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☐	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☐	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☒	☐	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☐	☒	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		

[4] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

[5] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH, CDRH-OC
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 9/15/2011, CMC – 10/26/2011 ***If yes, distribute minutes before filing meeting***	☒	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 10/22/2014, CMC – 12/16/14 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 17, 2015

BACKGROUND: sanofi submitted an original Biologic Licensing Application for sarilumab, a human IgG1 monoclonal antibody for use in treatment of patients with rheumatoid arthritis (RA). This memo documents the attendees and filing decisions for BLA 761037.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Christine Ford	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Janet Maynard		Y
Division Director/Deputy	Badrul Chowdhury/Sarah Yim		Y
Office Director/Deputy	Curt Rosebraugh/Mary Parks		N
Clinical	Reviewer:	Suzette Peng	Y
	TL:	Janet Maynard	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Jianmeng Chen, Sheetal Agarwal	Y
	TL:	Ping Ji	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Yongman Kim	Y

	TL:	Greg Levin	Y

APPEARS THIS WAY ON ORIGINAL

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Eleni Salicru	Y
	TL: ODE AD:	Tim Robison Tim McGovern	Y Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL: OBP:	Michele Dougherty Gerald Feldman	Y Y
	RBPM:	Melinda Bauerlien Kristine Leahy	N Y
• Drug Substance	Reviewer:	Candace Gomez Broughton	N
• Drug Product	Reviewer:	Lakshmi Narasimhan	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	Reyes Candau-Chacon Patricia Hughes	N Y
• Facility	Reviewer:	Laura Fontan	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer: TL:	Erin Hachey Mishale Mistry	Y Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orencia	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees	Sally Seymour, DSS, DPARP		Y
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☐ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☒ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Curtis Rosebraugh, MD, MPH **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 4/6/2016 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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/s/

CHRISTINE H FORD
09/30/2016

SANDRA L BARNES
09/30/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 28, 2016
To:	Badrul Chowdhury, MD, PhD Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	KEVZARA (sarilumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761037
Applicant:	Sanofi US Services Inc. on behalf of Sanofi-aventis U.S. LLC, A Sanofi Company

1 INTRODUCTION

On October 30, 2015, Sanofi US Services Inc. on behalf of Sanofi-aventis U.S. LLC, A Sanofi Company, submitted for the Agency's review an Original New Biologics Licensing Application (BLA) 761037 for KEVZARA (sarilumab) injection, for subcutaneous use. KEVZARA (sarilumab) is a New Molecular Entity (NME) with a proposed indication for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDS).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on February 8, 2016 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for KEVZARA (sarilumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on September 2, 2016.

2 MATERIAL REVIEWED

- Draft KEVZARA (sarilumab) injection, for subcutaneous use MG and IFUs received on October 30, 2015 and received by DMPP and OPDP on September 14, 2016.
- Draft KEVZARA (sarilumab) injection, for subcutaneous use Prescribing Information (PI) received on October 30, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on September 14, 2016.
- Draft KEVZARA (sarilumab) injection, for subcutaneous use Prescribing Information (PI) received on October 30, 2015, revised by the Review Division throughout the review cycle, and received by OPDP on September 13, 2016.
- Division of Medication Error Prevention and Analysis (DMEPA) Human Factors, Label, Labeling, and Packaging Review for BLA 761037 Kevzara (sarilumab) Injection 150 mg/1.14 mL, 200 mg/1.14mL dated September 2, 2016.
- Approved ACTEMRA (tocilizumab) comparator labeling dated October 21, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
09/28/2016

ADEWALE A ADELEYE
09/28/2016

MARCIA B WILLIAMS
09/28/2016

LASHAWN M GRIFFITHS
09/29/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 28, 2016

To: Christine Ford, MS, RPh, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)

Subject: BLA # 761037 – KEVZARA (sarilumab) injection, for subcutaneous use

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Reference is made to DPARP's consult request dated February 8, 2016, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, Medication Guide MG), and Instructions for Use (IFU) for KEVZARA (sarilumab) injection, for subcutaneous use (Kevzara).

OPDP has reviewed the proposed PI entitled, "761037 sarilumab uspi 090916 clean.docx" that was sent via e-mail from DPARP to OPDP on September 14, 2016. OPDP's comments on the proposed PI are provided directly on the attached mark-up copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- "carton-150mg-2ct-pfsyringe.pdf"
- "carton-200mg-2ct-pfsyringe.pdf"

that was submitted by sanofi-aventis U.S. LLC on June 14, 2016. OPDP has the following comments regarding the proposed Carton/Container labeling (attached below):

"OPDP is concerned [redacted] (b) (4)

(b) (4) In the absence of supporting evidence, OPDP recommends deleting this information from the carton/container labeling."

Please note that comments on the proposed MG and IFU will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
09/28/2016

HUMAN FACTORS, LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 2, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761037
Product Name and Strength:	Kevzara (sarilumab) Injection 150 mg/1.14 mL, 200 mg/1.14 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sanofi Genzyme
Submission Date:	October 30, 2015, March 9, 2016, June, 14, 2016
OSE RCM #:	2015-2746 and 2016-628
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Assoc. Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review evaluates the Human Factors (HF) validation study report, proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Kevzara (sarilumab) Injection (BLA 761037). The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the HF validation report and proposed labels and labeling as part of their evaluation of the 351a submission for Kevzara.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY

The Applicant performed an HF validation study to evaluate the use of the sarilumab prefilled syringe (PFS), the associated label and packaging, and the Instructions for Use (IFU). DMEPA previously reviewed the HF study protocol for the proposed PFS prior to the Applicant initiating the study[a]. We note that the Applicant implemented all of our recommendations and the methodology is acceptable.

During the HF validation study, there were failures that occurred with the following critical tasks:

1. Failure to wash hands (6/139 participants: 1 trained patient, 4 untrained patients, and 1 untrained caregiver)
2. Failure to clean injection site prior to injection (7/139 participants: 2 trained patients, 3 untrained patients and 2 untrained caregivers)

[a] IND 100632 Sarilumab Type C Meeting Minutes. 2013JUL02

3. Failure to press on plunger and inject the full dose (1/139 participants: 1 untrained caregiver)
4. Failure to dispose of device and needle cap in a safe manner: (28/139 participants: 14 patients and 14 caregivers)

Most of the failures were related to standard practice associated with this type of injectable product such as hand washing and cleaning injection site. With regard to the one failure to press on the plunger and inject the full dose, the untrained, injection naïve caregiver "pressed the plunger almost all of the way to the bottom of the syringe body and then removed the needle from the injection pad, and a very small amount of liquid remaining in the syringe emerged from the needle tip onto the injection pad." The participant realized that they removed the needle early from the injection pad and performed a second injection successfully. In addition, we noted that five patient participants (2 trained/injection experienced, 1 untrained/ injection naïve, 2 untrained/injection experienced) and four caregiver participants (1 trained/ injection experienced, 1 untrained/injection naïve, 2 untrained/injection experienced) had difficulties with this task. The subjective data indicated that some participants primed the needle before inserting it into the skin based on their previous injection experience. Other participants stated that 1) they had difficulty reaching for the plunger due to how far they needed to reach with their thumb, or 2) that they were unsure whether their thumb had enough strength to push the plunger, or 3) had trouble getting the correct grip on the device. However, despite these difficulties, all of these participants were able to successfully complete an injection during this study. We note that the design of the proposed prefilled syringe is standard for the indicated Rheumatoid Arthritis patient population and thus this patient population is accustomed to using this type of prefilled syringe. We also have determined that the use error and use difficulties associated with this task were attributed to first time use only, and do not have any recommendations at this time.

With regard to the failures to dispose of the device and needle cap in a safe manner, the subjective data indicated that these participants did not read the IFU, glanced over the IFU, or relied upon previous pre-filled syringe experience. However none of the errors resulted in a needle stick and our review of the IFU appears found that it specifically instructs the user to "*Put your used syringe and the cap into a puncture-resistant container*" and has an image of the user placing the cap and used syringe in a puncture-resistant container. As a result, we do not have any recommendations at this time.

There were other difficulties and failures reported amongst the non-critical tasks such as checking the expiration date, checking the drug condition, pinching the skin and inserting at 45 angles (see Appendix C (page 24) for a detailed description). The applicant reported that a revision to the IFU was made to further clarify the storage and checking drug information, which we found acceptable in address the observed issues seen in the study.

3.2 LABELS AND LABELING

In addition to the HF validation study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the Instructions for Use acceptable from a medication error perspective. However, we note that the carton labeling includes (b) (4)

Therefore, we recommend that (b) (4) should be removed from the carton labeling.

We also note that the container labels and Prescribing Information can be improved to increase the readability and prominence of important information to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information. We provide recommendations in Section 4.1 for the Prescribing Information and 4.2 for the container label, and carton labeling to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the HF validation study acceptable. DMEPA also finds the Instructions for Use acceptable from a medication error perspective. However, our review indicates that the proposed Prescribing Information, container labels and carton labeling can be improved to increase the readability and prominence of important information. Please see our recommendations in sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights and Full Prescribing Information

1. Per ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations, consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion**.**

B. Full Prescribing Information: Section 16 How Supplied

1. The NDC number is denoted by a placeholder (XXXXX-XXXX-XX). Ensure the applicant submits the actual NDC number.

4.2 RECOMMENDATIONS FOR SANOFI GENZYME

We recommend the following be implemented prior to approval of this BLA:

A. All labels and labeling (Container Label, Carton Labeling)

1. The NDC number is denoted by a placeholder (XXXXX -XXXX-XX). Submit the actual NDC number and ensure that the middle 4 digits (XXXX) are different between the strengths.

B. All Carton Labeling

1. Remove [redacted] (b) (4) wherever presented.
2. The strength statement is not presented consistently in accordance with USP General Chapter <1>. Wherever presented, the strength statement should be as follows:

150 mg/1.14 mL or 200 mg/1.14 mL

C. All Container Labels

1. Ensure that the barcode is scannable. Consider reorienting the barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Kevzara that Sanofi submitted on October 30, 2015 and March 9, 2016.

Table 2. Relevant Product Information for Kevzara	
Initial Approval Date	N/A
Active Ingredient	Sarilumab
Indication	treatment of rheumatoid arthritis in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	150 mg/1.14 mL, 200 mg/1.14 mL
Dose and Frequency	• 200 mg once every two weeks • 150 mg once every two weeks is recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes
How Supplied	Supplied as a sterile, preservative-free liquid solution in a single-dose pre-filled syringe (2 syringes per pack).
Storage	Refrigerate at 36◦F to 46◦F (2◦C to 8◦C). Do not freeze.

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APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 1, 2016 we searched the L:drive and AIMS using the term, sarilumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous proprietary name reviews that are not relevant to this review.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Use-Risk analysis

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
1.1	Pharmacist stores product in a refrigerator	Pharmacist stores the syringe incorrectly.	This could lead to: • Ineffective drug; • Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Storage conditions clearly displayed on the package	Ask a question in HF validation study about proper device storage.
1.2	Pharmacist dispenses product to the patient	Pharmacist selects the wrong package and dispenses a drug for another disease instead of sarilumab.	This could lead to: • Fatal adverse reaction following administration of other drug (e.g. severe hypoglycemia following insulin administration or anaphylactic reaction to drug). Severity: Very serious, depending on the specific drug dispensed if injected and the specific patient's sensitivity	Distinctive packaging: • Unique label color and visual appearance	Include package differentiation task in HF validation study.
		Pharmacist selects the wrong package and dispenses a different anti-RA drug instead of sarilumab.	This could lead to: • Adverse reaction to the other anti-RA drug. Severity: Significant, depending on the specific drug dispensed if injected and the specific patient's sensitivity		
		Pharmacist selects the wrong package and dispenses wrong dose of sarilumab (150 mg instead of 200 mg).	This could lead to: • Full effect of drug on RA symptoms may not be achieved (i.e., symptoms may not improve but should not worsen). Severity: Negligible to no harm		

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
		Pharmacist selects the wrong package and dispenses wrong dose of sarilumab (200 mg instead of 150 mg).	This could lead to: • Decrease in neutrophil count, • Increase in some hepatic and lipid parameters. Severity: Marginal		
		Pharmacist does not check the expiration date of the drug.	This could lead to: • Ineffective drug; • Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Expiration date is clearly displayed on the package.	Ask a question in HF validation study regarding the expiration date on the package.
1.3	Patient to store the product in a refrigerator	User stores the syringes in inappropriate conditions.	This could lead to: • Ineffective drug; • Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Storage information clearly displayed in the IFU and on the package	Ask a question in HF validation study about proper device storage.
		User does not know that device should be kept out of reach of children.	This could lead to: • Sharps injuries, • Swallowing or inhalation of small parts • Drug administration to an unintended person Severity: Very serious	Storage information clearly displayed in the IFU and on the package.	This hazard exists for all syringes. Therefore, this is not a part of the assessment.

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
2.1	Select package, open packaging and remove device	User selects the wrong package, which contains a drug for another disease instead of sarilumab.	This could lead to: • Fatal adverse reaction following administration of other drug (e.g. severe hypoglycemia following insulin administration or anaphylactic reaction to drug). Severity: Very serious, depending on the specific drug injected and the specific patient's sensitivity	Distinctive packaging: •Unique label color and visual appearance	Include package differentiation task in HF validation study.
		User selects the wrong package, which contains a different anti-RA drug instead of sarilumab.	This could lead to: • Adverse reaction to the other anti-RA drug. Severity: Significant, depending on the specific drug injected and the specific patient's sensitivity		
		User selects the wrong package and injects the wrong dose of sarilumab (150 mg instead of 200 mg).	This could lead to: • Full effect of drug on RA symptoms may not be achieved (i.e., symptoms may not improve but should worsen). Severity: Negligible to no harm		
		User selects the wrong package and injects the wrong dose of sarilumab (200 mg instead of 150 mg).	This could lead to: • Decrease in neutrophil count, • Increase in some hepatic and lipid parameters Severity: Marginal		
		User fails to open packaging and cannot use the device.	The patient receives no dose of the drug. Severity: Marginal (in single incidence)	Package is designed for easy opening	Include package opening and syringe retrieval tasks in HF validation study.
		User fails to remove the syringe safely (e.g. syringe drops) and cannot use the device.	The patient receives no dose of the drug. Severity: Marginal (in single incidence)	Package is designed for easy removal of device	

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
2.2	Select correct syringe	User selects the wrong syringe and injects a drug for another disease instead of RA.	This could lead to: •Fatal adverse reaction following administration of other drug (e.g. severe hypoglycemia following insulin administration or anaphylactic reaction to drug) Severity: Very serious, depending on the specific drug dispensed and the patient's sensitivity.	Distinctive device label: •Unique label color and visual appearance •Unique finger flange color	Include task in HF validation study.
		User selects the wrong syringe and injects another anti-RA drug instead of sarilumab.	This could lead to: •Adverse reaction to the other anti-RA drug. Severity: Significant, depending on the specific drug dispensed and the patient's sensitivity.		
		User selects the wrong package and injects the wrong dose of sarilumab (150 mg instead of 200 mg).	This could lead to: •Full effect of drug on RA symptoms may not be achieved (i.e., symptoms may not improve but should not worsen). Severity: Negligible to no harm.		
		User selects the wrong syringe and injects the wrong dose of sarilumab (200 mg instead of 150 mg).	This could lead to: •Decrease in neutrophil count, •Increase in some hepatic and lipid parameters. Severity: Marginal.		

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
2.3	Check expiration date	User does not know that he has to check the expiration date of the drug.	This could lead to: •Ineffective drug; •Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Expiration date is clearly displayed on the package and on the syringe label.	Ask a question in HF validation study regarding the expiration date of the syringe.
2.4	Check drug condition	User does not know that he has to check the visual appearance of the drug.	This could lead to: •Ineffective drug; •Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Information is clearly presented in the IFU	Ask a question in HF validation study about how to tell if the drug in the syringe is okay to use.
2.5	Warm up at room temperature for at least 30 minutes	User does not wait (at least for 30 minutes) for the PFS to warm up before the injection.	This could lead to: underdose due to high viscosity: • Worsening of underlying RA symptoms (e.g. disease flare, pain or swelling of joints, morning stiffness, etc.) Severity: Marginal if too high injection force leads to single underdose	Information is clearly presented in the IFU	Ask a question in HF validation study about how and for how long to warm up the syringe.
		User warms up the syringe at too high a temperature or for too long or does not keep the syringe out of sunlight before using it.	This could lead to: • Ineffective drug; Potential for increased risk of immunogenicity (Anti-drug antibodies). Severity: Marginal	Information is clearly presented in the IFU	

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
2.6	Choose correct injection site	User chooses an incorrect location for subcutaneous administration.	This could have an insignificant effect on pharmacokinetics.	Information is clearly presented in the IFU	Ask a question in HF validation study about where to inject.
2.7	Prepare for injection	User performs the injection without washing hands or cleaning the injection site with alcohol wipe.	This could lead to: Infection or reaction (e.g. skin) to the contamination Severity: Significant	Information is clearly presented in the IFU	Ask a question in HF validation study about where to inject.
3.1	Remove the needle cap	User cannot remove the needle cap (because the force required is too high).	This could lead to: • Worsening of underlying RA symptoms (e.g. disease flare, pain or swelling of joints, morning stiffness, etc.) Severity: Significant, in the event of repeated incidences of no dose injected	Needle cap is standard for this type of syringe.	Include needle removal task and injection tasks in HF validation study.
		User does not inject immediately after removing the cap.	This could lead to: • Worsening of underlying RA symptoms (e.g. disease flare, pain or swelling of joints, morning stiffness, etc.) Severity: Significant, in the event of repeated incidences of no dose injected	Information in the IFU about when to remove the needle cap	
		User handles the uncapped syringe carelessly.	This could lead to: • Contamination of the device (needle) Severity: Significant	This hazard exists for all syringes.	

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
3.2	Pinch skin and insert needle fully at roughly a 45°angle	User does not insert the needle fully.	Depending on amount of drug delivered subcutaneously, this could lead to underdose: • Worsening of underlying RA symptoms (e.g. disease flare, pain or swelling of joints, morning stiffness, etc.). Severity: Negligible to no harm	Information on how to perform the injection is clearly displayed in the IFU	Include injection task in HF validation study.
		User does not pinch a fold of skin.	This could lead to: • Painful injection (intra-muscular injection). Severity: Marginal		
		User presses plunger before inserting the needle into the skin.	This could lead to: • Underdose Severity: Significant, in the event of repeated incidences of underdose.		
3.3	Press on plunger and inject full dose	User does not push the plunger as far as it will go.	This could lead to underdose. Severity: Significant, in the event of repeated incidences of underdose.	Syringe is designed with a transparent syringe barrel that shows the progression of the drug delivery	Include injection task in HF validation study.
		Injection forces are too high for user population.		Syringe is designed with an ergonomic finger flange and a large plunger for easy injection.	
		User tries to remove air bubbles prior to injection.		Information clearly presented in the IFU to not attempt to remove air bubbles	

Task No.	Task	Potential Use error	Most Serious Potential Harm & Severity	Mitigation	Evaluation
3.4	Remove needle from the skin	User removes the needle from the skin without due caution.	This could lead to a third party receiving a needle stick injury, which could transmit a severe blood-borne disease (e.g. HIV, Hepatitis B & C). Severity: Very serious	This hazard exists for all syringes. Information on how to perform the injection is clearly presented in the IFU.	Include injection task in HF validation study.
4.1	Discard device and needle cap in a safe manner	Disposal of used syringes into domestic waste.	This could lead to a third party receiving a needle stick injury, which could transmit a blood-borne severe disease (e.g. HIV, Hepatitis B &C). Severity: Very serious	This hazard exists for all syringes. Information on proper device disposal clearly presented in the IFU.	Include device discarding task in HF validation study.
		Nurse or lay caregiver re-caps the needle	This could lead to the user receiving a needle stick injury, which could transmit a severe blood-borne disease (e.g. HIV, Hepatitis B & C. Severity: Very serious		

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Participants

Table 18 - Participants involved in the HF validation study

User group (n = # of participants)	Sub-groups (if any)	Description (n = # of participants)	Study tasks		
			Differentiation	Handling	IFU
Moderate to severe RA Patients (n=62) Self-reported: • 93% had moderate to severe RA • 46% had hand/dexterity impairments • <1% had vision impairments • <1% had hearing impairments		Untrained and syringe-naive[a] (n=15)	x	x	x
		Untrained but experienced in self-injection with a syringe (n=15)	x	x	x
		Trained and syringe-naive (n=15)	x	x	x
		Trained and experienced in self- injection with a syringe (n=17)	x	x	x
Non-professional (layperson) caregivers (n=62)		Untrained and syringe-naive[a] (n=16)	x	x	x
		Untrained but experienced in injection with a syringe (n=15)	x	x	x
		Trained and syringe-naive (n=15)	x	x	x
		Trained and experienced in injection with a syringe (n=16)	x	x	x
Nurses currently administering/training RA patients (n=15)		Untrained but syringe-experienced	x	x	x
Pharmacists (n=15)			x	-	-

a The syringe naïve participants might have had (but were not required to have) previous experience with another type of injection device, such as a pen or autoinjector.

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Training

In this study, 32 patients and 31 lay caregivers were trained. All the untrained participants (30 patients and 31 lay caregivers), including all 15 nurses and all 15 pharmacists, were given only a high-level overview of the purpose of the therapy and the study.

- Prior to the syringe packaging differentiation task and the syringe differentiation task, the participants were shown the PFS and its packaging.
- Prior to the syringe handling tasks, the participants were given the syringe packaged in an unopened box (ie, as it would be when they received it from the pharmacist). The moderator instructed the participant to do what they would normally do upon receiving and using the syringe for the first time. The participants were instructed to inform the moderator when they were ready to proceed with the tasks.

The trained participants received a simple training on how to use the device.

- In a one-on-one session, the moderator gave the participant the IFU and talked him or her through all of the content of the document, answering any questions as they arose. The participants were then asked to use the PFS to perform an injection into an injection pad. The moderator answered questions and provided guidance as needed for the participant to complete the injection successfully.
- Each trained participant was asked to return 7 to 10 days later to perform the differentiation and handling tasks and the IFU assessment. All participants were given the IFU to take home with them.

Test Procedures

Table 20 provides an overview of the procedures for each participant. The trained participants were trained in a separate session 7–10 days prior to the test session.

Table 20 - Overview of a test session

Task	Procedures		Patients	Lay Caregivers	HCPs	
					Nurses	Pharmacists
Welcome, Informed Consent and Participant Assessment	A receptionist welcomed the participant. The participant signed an informed consent form that described the study's intent, procedures, as well as the participant's right to withdraw from the study at any time.		x	x	x	x
RAPID 3 assessment	The patient participants were asked to complete the RAPID3 questionnaire (Appendix 6) on a computer, to facilitate score calculation; the study staff assisted any participant who needed or wanted it. The participant was escorted then to the testing room and seated at a table.		x	-	-	-
9. Introduction	The study moderator provided a general introduction to the drug, device and dosing regimen and introduced the participant to the PFS packaging and syringe.		x	x	x	x
1. Product Differentiation	**A: Select correct package**	**Conditions:** The target package, the package with the other dose of sarilumab, and the comparator packages were already placed in the refrigerator. All Patients and Lay Caregivers: Low lighting Nurses and pharmacists: Normal lighting **Instruction:** Patients, Nurses, Lay Caregivers and Pharmacists: The moderator asked the participant to get the PFS package from the refrigerator. Note: Half of the participants in each user group were asked to find the PFS package for the 150 mg dose and the other half was asked to find the PFS package for the 200 mg dose.	x	x	x	x
	B: Select correct syringe	**Conditions:** The target syringes, the syringe with the other dose of sarilumab, and the comparator syringes were already placed in the refrigerator All patients and Lay Caregivers: Low lighting Nurses: Normal lighting **Instruction:** Patients, Nurses and Lay Caregivers: The moderator asked the participant to get the PFS from the refrigerator. Note: Half of the participants in each user group was asked to find the PFS for the 150 mg dose and the other half was asked to find the PFS for the 200 mg dose.	x	x	x	-
2. Device Handling	**Conditions:** The moderator asked all participants to give the unaided injection, and intervened only in case of potential harm for the participant to complete the injection successfully. All participants (including those that were trained) were asked to perform the handling tasks and participants provided a subjective narrative about using the device, including their perceptions of any use errors or difficulties they had or any comments about using the syringe. The moderator asked the participants specifically about all use errors (including task failures) that occurred to ascertain his or her perspective on the possible reasons for each problem and how the device or the labeling could be designed to avoid the problem.		x	x	x	-
3. IFU Assessment	**Instructions:** All patients, Nurses and Lay Caregivers: The moderator asked each participant to review the IFU, answer a set of open-ended questions, and provide comments about the IFU. Participants were asked to find information about selected critical facts in the IFU, such as the warnings, and to explain in their own words what they mean. The moderator recorded the participant's answers, which were later assessed for correctness and completeness.		x	x	x	-
4. Ishihara Test	At the end the participants were also asked to take the Ishihara Test (Appendix 7), which assesses color vision.		x	x	x	x

C.2 Results

Errors (failures/difficulties) for critical tasks

a. Selects the correct syringe

User selects the wrong syringe and injects the wrong dose of sarilumab (200 mg instead of 150 mg). This could lead to: • Decrease in neutrophil count, • Increase in some hepatic and lipid parameters.	Marginal	Difficulty	1/62 patient	The moderator initially gave P13 (untrained/naïve) the wrong device (200 mg instead of 150 mg), then realized it, and gave P13 the correct device. When P13 went to the refrigerator, he initially selected the incorrect device, choosing the 200 mg syringe instead of the 150 mg syringe. He realized as soon as he returned to the table that he had selected the incorrect device. He said that he should have chosen the other (150mg) syringe.	The participant may have been confused by the moderator about which device he was being asked to retrieve.

b. Wash hands/clean site

Prepare for injection "wash hands"	User performs the injection without washing hands or cleaning the injection site with alcohol wipe. This could lead to: • Infection or reaction (eg, skin) to the contamination	Significant	Pass	57/62 patients 61/62 care-givers 15/15 nurses	-	-
			Use error	5/62 patients	**5 patients** [[2 trained naïve (P17, P20), 2 untrained/naïve (P50, P31), and 1 untrained/exp. (P18)] **did not wash their hands.** Trained (2/5 errors): P17 (trained/naive) said he only looked at the pictures and not the words when reading the IFU, which caused him to miss the step in the IFU about washing hands. P20 (trained/naive) said she bypassed the instruction in the IFU because the sink in the testing room was not operational. Untrained (3/5 errors): P18 (untrained/exp.) and P50 (untrained/naive) said they normally would give injections after a shower, so they assumed that their hands were already clean based on previous injection experience. P31 (untrained/naive) said she was aware that she needed to wash her hands, but it slipped her mind during the injection task.	Due to the artificial nature of the test situation, participants may assume that there is no need to wash hands. This would be considered to be a test artifact of the simulated use situation. Users may choose to skip this task or not pay attention to the preparation steps in the IFU or not refer to the IFU before the injection procedure. This use error is known to exist for all syringe devices. In the IFU assessment part of the study, all the patient participants were able to find and understand this information in the IFU, which indicates that the IFU is adequate.

		Use Error	1/62 care-givers	1 lay caregiver (C23 untrained/ exp.) did not wash his hands. When asked why, he stated that he does not always wash his hands when giving injections with other devices.	Since this participant stated that he would not always wash his hands, it is not likely that he would have washed hands in this study. His comment indicated that he knew he was supposed to; this error can be attributed to his injection practice with other devices. In the IFU assessment part of the study, this participant was able to find and understand this information in the IFU, which indicates that the IFU is adequate.
User performs the injection without washing hands or cleaning the injection site with alcohol wipe. This could lead to: • Infection or reaction (eg, skin) to the contamination	Significant	Pass	57/62 patients 60/62 care-givers 15/15 nurses	-	-
		Use error	5/62 patients	5 patients [1 trained/naïve (P62), 1 trained/exp. (P34), 2 untrained/naïve (P50, P17), 1 untrained/exp. (P60)] did not clean the injection site.	This use error is known to exist for all syringe devices.

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				Trained (2/5 errors): P34 (trained/exp.) said she was distracted by giving the injection, and forgot to disinfect the injection site. P62 (trained/naive) said she had taken a shower in the morning, so she assumed her hands and body were clean. Untrained (3/5 errors): P50 (untrained/naive) said she "skimmed" the instructions just to see how to operate the syringe, and passed over the instruction about disinfecting the injection site. P60 (untrained/exp.) removed the wipe from the box and placed it on the table, but did not use the wipe. She said she read the instruction to gather the materials to give the injection, but not when to use the alcohol wipe during the injection process. P17 (untrained/naive) stated that he only looked at the pictures but not the words in the IFU.	Due to the artificial nature of the test situation, participants may assume that there is no need to clean injection site because they are injecting into a pad and not into real skin. This would be considered to be a test artifact of the simulated use situation. Users may skip this task and not pay attention to this information in the IFU or not refer to the IFU before the injection procedure. In the IFU assessment part of the study, all the patient participants were able to find and understand this information in the IFU, which indicates that the IFU is adequate.
		Use error	2/62 care-givers	2 untrained lay caregivers [1 untrained/exp. (C23), 1 untrained/naïve (C40)] did not clean injection site. C23 said he usually uses an alcohol swab when giving an injection, but did not in this case. C40 initially read through the whole IFU before proceeding with the injection, then read the IFU while she gave the injection, but passed over the step to disinfect the injection site.	This use error is known to exist for all syringe devices. Users may skip this task and not pay attention to this information in the IFU or not refer to the IFU before the injection procedure. In the IFU assessment part of the study, all the caregivers participants were able to find and understand this information in the IFU, which indicates that the IFU is adequate.

c. Failure to remove cap

Remove the needle cap	Failure to remove the needle cap could lead to: • Worsening of underlying RA symptoms (eg, disease flare, pain or swelling of joints, morning stiffness, etc.)	Significant, in the event of repeated incidences of no dose injected	Pass	61/62 patients 61/62 care-givers 15/15 nurses	-	-
	Failure to inject immediately after removing the cap could lead to a blocked needle and higher injection forces; if no dose is delivered: • Worsening of underlying RA symptoms (eg, disease flare, pain or swelling of joints, morning stiffness, etc.). User handles the uncapped syringe	Significant, in the event of repeated incidences of no dose injected Significant	Difficulty	1/62 patient	1 patient (P05, trained/naive) initially tried removing the needle cap while holding the plunger, but then self-corrected and held the syringe body while pulling off the needle cap. She explained that she switched her grip because the device felt fragile when held by the plunger.	The cause of this difficulty is related to this participant's lack of experience using syringes and was not caused by the device user interface.
	carelessly. This could lead to: • Contamination of the device (needle)			1/62 care-givers	1 caregiver (C13 trained/naive) removed the needle cap, and then placed the syringe back on the table with the needle exposed. She realized during the injection that she had removed the cap too early, but she knew she had to prepare the injection site before inserting the needle.	While this participant was trained, the cause of this difficulty may be related to this participant's lack of experience using syringes and was not caused by the device user interface. This participant realized that she removed the cap early, which demonstrates that she was able to learn quickly how to use the syringe correctly.

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d. Deliver dose

Press on plunger and inject full dose	Pressing the plunger before inserting it into the skin could lead to: • Underdose.	Significant, in the event of repeated incidences of underdose	Pass	57/62 patients 57/62 care-givers 15/15 nurses	-	-
			Difficulty	5/62 patients	**5 patients** [2 trained/exp. (P25, P39), 1 untrained/naïve (P48), 2 untrained/exp. (P16, P60)] **had difficulties with this task.**	For the experienced participants, these difficulties can be attributed to their prior experience with syringes. For the inexperienced participant, this difficulty can be attributed to lack of experience using syringes.
					Trained (2/5 errors): P25 (trained/exp.), P39 (trained/exp.), struggled to depress the plunger during the injection. P25 said she had difficulty reaching for the plunger due to how far they needed to reach with their thumb. P39 struggled to fully depress the plunger; her hand was shaking when she started to depress the plunger. Untrained (3/5 errors): P16 (untrained/exp.), P60 (untrained/exp.) primed the needle before inserting the needle into skin. They said they used their experience from previous injection devices. P48 (untrained/naïve) struggled to depress the plunger during the injection. P48 said she needed to use the base of the thumb because she was unsure if her thumb had enough strength to push the plunger in.	Such errors are not uncommon while users learn to operate new devices.
			Difficulty	4/62 Care-givers	**4 caregivers** [1 trained/exp. (C60), 1 untrained/naïve (C30), 2 untrained/exp. (C20, C25)] **had difficulties with this task.**	These difficulties can be attributed to participants' prior experience with syringes.

					Trained (1/4 errors): C60 (trained/exp.) primed the needle before inserting the needle into skin. C60 said she used her experience from previous injection devices. Untrained (3/4 errors): C20 (untrained/exp.) and C25 (untrained/exp.) had their thumb on the plunger before inserting the needle. C20 said that it was her first time using the device and had trouble getting the correct grip on the device. C25 said that she normally sees some medication leave the syringe before she gives injections due to back pressure in the syringe. C30 (untrained/naïve) primed the needle before inserting the needle into skin. C30 said the needle needed to be primed based on her experience watching injections on television.	For C20, this difficulty can be attributed to first time use of the syringe.
			Use error	1/62 care-giver	**1 caregiver** (C13, untrained/naive), during the injection, pressed the plunger almost all of the way to the bottom of the syringe body and then removed the needle from the injection pad, and a very small amount of liquid remaining in the syringe emerged from the needle tip onto the injection pad. This participant immediately realized that she removed the needle from the injection pad early.	This error can be attributed to lack of experience using syringes. Such errors are not uncommon while users learn to operate new devices. The participant was able to learn quickly how to use the device correctly.

e. Discard device

Discard device and needle cap in a safe manner	This could lead to a third party receiving a needle stick injury, which could transmit a blood-borne severe disease (eg, HIV, Hepatitis B &C).	Very serious	Pass	48/62 patients 47/62 care-givers 15/15 nurses	-	-

			Use error	14/62 patient	**14 patients** [1 trained/naïve (P22), 1 trained/exp. (P43), 4 untrained/naïve (P17, P19, P49, P53), 8 untrained/exp. (P12, P15, P16, P18, P48, P51, P59, P60)] **re-capped or attempted to re-cap the device and**, for safety reasons, were stopped by the moderator before the error could occur. <u>Trained (2/14 errors):</u> P22 (trained/naïve) explained that she re-capped other devices she used to inject medication. P43 (trained/exp.) said that her previous injection experience caused her to re-cap the device <u>Untrained (12/14 errors):</u> P12, P15 (untrained/exp.) said that their previous injection experience caused them to re-cap the device. P16 (untrained/exp.) saw the instruction to discard the device, but thought it was safer to re-cap the device and that an exposed needle could be dangerous. P17 (untrained/naïve) only looked at the pictures in the IFU when giving the injection; therefore he missed the instruction to not re-cap the device. P18 (untrained/exp.) did not read the IFU during her first injection; even after reading the IFU during her second injection, she still re-capped. P19 (untrained/naïve) said she would re-cap because she would be afraid to stick herself when emptying the trash, if she did not have a puncture resistant container and had to throw the syringe out in the trash. P48 (untrained/exp.) found the instruction after the injection was completed, and said she was only "glancing" at the instructions before she delivered the injection. P49 (untrained/naïve) knew the IFU said not to re-cap, but forgot the instruction when she had to concentrate on giving the injection.	No needle stick injuries were observed in this study. These use errors are recognized to exist for all syringes. For the experienced participants, these errors can be attributed to their prior experience with syringes. The participants who read the IFU knew what they were supposed to do, but some of the participants who did not read the IFU were not aware of safe handling procedures for syringes.

					P51, P59 (untrained/exp.) said they felt more comfortable if the needle was capped than if it was exposed after giving an injection. P53 (untrained/naïve) said she only saw the instruction to place the needle in a sharps container, and did not read the instruction saying not to re-cap the device. P60 (untrained/exp.) said she would re-cap because the "gloves made me feel like I had extra protection" and that she wanted to put the device in the sharps container in the same condition as when she pulled it out of the box.	
			Use error	15/62 care-givers	**13 caregivers**, all untrained (C15, C17, C22, C25, C30, C31, C32, C33, C34, C35, C37, C38, and C51) **recapped or attempted to re-cap the device after using it** (but, for safety reasons, were stopped by the moderator before the error could occur). **2 caregivers**, both untrained (C18 and C25), **discarded the syringe into the trash can.**	No needle stick injuries were observed in this study. These use errors are recognized to exist for all syringes. For the experienced participants, these errors can be attributed to their prior experiences with syringes.
					<u>Discarding the syringe into the trash can instead of the sharps container (2/15 errors):</u> C25 (untrained/exp.) said she usually throws her needles into a separate trash can from her normal household trash, instead of discarding the device into a sharps container. C18 (untrained/naïve) was given a second device to perform an injection with (due to injecting at an incorrect angle), and discarded the device properly after reading the IFU a second time. <u>Re-capping or attempting to re-cap the device (13/15 errors):</u> <u>All untrained (6 exp., 7 naïve):</u> C15 (untrained/exp.) said she would re-cap the device if it was being thrown into household trash in order to protect her pets. C25 (untrained/exp.) said she does not normally re-cap syringes after she is using them, and that she recapped the device due to being in a simulated use situation.	The participants who read the IFU knew they were not supposed to re-cap. Some of the participants who did not read the IFU were not aware of safe handling procedures for syringes.

					C32 (untrained/exp.) said that she felt more comfortable if the needle was capped than if it was exposed after giving an injection. C33 (untrained/exp.) explained that she re-capped other devices she used to inject medication. C35 (untrained/exp.) did not read IFU when giving her first injection; during her second injection she read the IFU and did not re-cap the device. C37 (untrained/exp.) said that she noticed the IFU said not to re-cap the device, but she "just kind of did it." C17 (untrained/naïve) said that all needles should be re-capped, and that the cap should be able to be placed back on the needle in case of interruptions while injecting the medication. C22 (untrained/naïve) said the needle needed to be re-capped before it was discarded, but thought it would be sufficient to use a waste receptacle with a removable bag. C30 (untrained/naïve) said she re-capped the device so the needle would not be exposed, and that the instructions told her to cover the needle with the cap.	
					C31 (untrained/naïve) explained that she re-capped other devices she had used to inject medication. C34 (untrained/naïve) thought the IFU said to re-cap. When she reread the IFU, she found and understood that the device was not supposed to be re-capped. She said she would re-cap needles at home because she does not have a sharps container and would throw it into the trash. C38 (untrained/naïve) was stopped by the moderator while attempting to re-cap during her first injection and said "it would not fit anyway." She was given another device to inject, and she did not recap that device after injecting the medication successfully. C51 (untrained/naïve) said she understood that the IFU said not to re-cap, but that it was her first time using a syringe and she thought that re-capping "is what you are supposed to do."	

IFU assessment failures

Q 4.1 for patients: After you use the syringe, what should ou do with the syringe and the needle cap? Correct answer: *"Discard them into a sharps container"*	Not knowing how to dispose of used syringes, could lead to a third party receiving a needle stick injury, which could transmit a blood-borne severe disease (eg, HIV, Hepatitis B &C).	Very serious	Pass	61/62 patients 59/62 care-givers 15/15 nurses	-	-
			Use error	1/62 patient	1 patient (P17 untrained/naïve) did not refer to the IFU when answering this question. He said that he would bend or break the syringe before disposing of it in a container.	Because the moderator did not ask the participant to look at the IFU, this question tested the participant's memory and not the adequacy of the IFU, as intended.
			Use error	3/62 care-giver	2 lay caregivers (C09 trained/exp., C25 untrained/exp.) did not refer to the IFU answering this question. C09 and C25 said that they would throw the device away in their household trash. 1 lay caregiver (C30 untrained/naïve) did refer to the IFU after being asked the question, and then answered incorrectly. C30 said that she would throw the device away in household trash. She did notice later that the IFU said to throw the device away into a "puncture resistant container", not the household trash.	C09, C25: because the moderator did not ask the participant to look at the IFU, this question tested the participant's memory and not the adequacy of the IFU, as intended. C30: This participant might have initially skipped this information in the IFU and thus was not aware of safe handling procedures for syringes. She was able to find the information in the IFU eventually.

f. Non-critical task failures occurred amongst checking the expiration date, checking the drug condition, pinching the skin and inserting at 45 angles. Per the applicant, a revision to the IFU was made to further clarify the storage and checking drug information and they also noted that training reduced the errors. Some participants didn't read the IFU, others read the IFU but chose not to follow the instructions as directed because they were injecting into an injection pad and others rely on previous experience with other devices where they didn't have to pinch or hold at an angle.

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/s/

TERESA S MCMILLAN
09/02/2016

MISHALE P MISTRY
09/02/2016

QUYNHNHU T NGUYEN
09/02/2016

LUBNA A MERCHANT
09/02/2016

CLINICAL INSPECTION SUMMARY

Date	July 15, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Susan D. Thompson, M.D. Team Leader, for Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Suzette Peng M.D., Medical Officer Janet Maynard, M.D., Clinical Team Leader Christine Ford, M.S., R.Ph., Regulatory Project Manager
BLA	761037
Applicant	Sanofi-Aventis
Drug	Sarilumab
NME	Yes
Therapeutic Classification	NME
Proposed Indication	Rheumatoid Arthritis
Consultation Request Date	February 12, 2016
Summary Goal Date	June 30, 2016 Extension: July 15, 2016
Action Goal Date	October 30, 2016
PDUFA Date	October 30, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For BLA 761037, three clinical sites (Drs. Aelion, Lee, and Kaine) were selected for audit and inspection. The sponsor (Sanofi-Aventis) was also inspected. The final classification for the inspection of Drs. Kaine is No Action Indicated (NAI).The preliminary classification for the inspections of the sponsor (Sanofi-Aventis) and Dr. Lee, is No Action Indicated (NAI) based on communications with the field investigator. The classification for the inspection of Dr. Aelion is No Action Indicated (NAI) for Study Protocol EFC11072 (Part B) [Final regulatory classification for all the studies inspected is pending]. The study data derived from these clinical sites and sponsor are considered reliable in support of the requested indication.

2. BACKGROUND

Sarilumab is a human IgG1 monoclonal antibody (mAb) that binds to the alpha-subunit of the IL-6 receptor, inhibiting the inflammatory effects of IL-6. Since IL-6 is a key cytokine in causing inflammatory changes and destruction of joints in rheumatoid arthritis, its inhibition may be one therapeutic approach for preventing further rheumatoid arthritis degenerative changes.

Two randomized clinical trials were submitted in support of the applicant's BLA for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more disease modifying anti rheumatic drugs (DMARDs).

For this BLA under the PDUFA V program review, for sarilumab, a New Molecular Entity (NME) therapeutic biologic for the treatment of rheumatoid arthritis, CDER DPARP requested three domestic sites for inspection. These sites principally enrolled large numbers of patients.

STUDY EFC11072 (Part B)

Study EFC11072 (Part B) was a randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study, to evaluate efficacy and safety of sarilumab (SAR153191, IL-6Rα mAb) plus methotrexate (MTX) in active rheumatoid arthritis patients, who are inadequate responders to MTX therapy. The objective of the study was to demonstrate that sarilumab added to MTX is effective in (1) reduction of signs and symptoms of RA at 24 weeks, (2) inhibition of progression of structural damage at 52 weeks, and (3) improvement in physical function at 16 weeks. The primary efficacy endpoints included the following: (1) ACR20 response at Week 24 (American College of Rheumatology [ACR 20] is the 20% improvement criteria in treatment response, comparing disease activity at two discrete time points), (2) change in modified Van der Heijde total Sharp score at Week 52 (Sharp score is a radiographic measure of disease progression), (3) change in physical function as measured by the change from baseline in the Health Assessment Question-Disability (HAQ-DI) at Week 16.

This study was conducted at 199 sites in Europe, North America, Asia, Australia, New Zealand,and South Africa. A total of 1116 patients [372 study subjects per arm] were planned to be enrolled for Cohort 2 (Part B). There were 1197 patients who were randomized in Cohort 2 (Part B). For Cohort 2 (part B): 398 study subjects received placebo, 400 study subjects received sarilumab 150 mg q2w treatments, and 399 study subjects received sarilumab 200 mg q2w. The first patient was enrolled on March 7, 2011 and the last patient completed on October 8, 2013.

STUDY EFC10832

Study EFC10832 was a randomized, double-blind, parallel, placebo-controlled study assessing the efficacy and safety of sarilumab (SAR153191, IL-6Rα mAb), added to non-biologic DMARD therapy in rheumatoid arthritis patients, who are inadequate responders to or intolerant of TNF-α antagonists. The primary study objective was to demonstrate that sarilumab added to non-biologic disease modifying anti rheumatic drugs (DMARDs) is effective for (1) reduction of rheumatoid arthritis signs and symptoms at week 24 and (2) improvement of physical function at week 12. The co-primary study endpoints were (1) ACR20 response rate at week 24 (i.e., the percentage of patients who at Week 24 achieve a 20% improvement from baseline, in the American College of Rheumatology (ACR) core set disease activity index), and (2) change in physical function as measured by the average of change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12.

This study was conducted at 240 sites worldwide. A total of 522 patients were planned to be enrolled. There were 546 study subjects who were randomized and who were treated. The first study subject was enrolled in October 29, 2012 and the last study subject completed the study in March 23, 2015.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Jacob Aelion, M.D. West Tennessee Research Institute 369 N. Pkwy. Suite 400 Jackson, TN 38305	Site 840025 Study Protocol EFC11072 (Part B) 15 enrolled subjects	March 15- 25, 2016	NAI
Eric Lee, M.D. Inland Rheumatology Clinical Trials, Inc. 1238 East Arrow Hwy Upland, CA 91786	Site 840049 Study Protocol EFC10832 7 enrolled subjects	April 18-20, 2016	Pending: Preliminary NAI
Jeffrey Kaine, M.D. Sarasota Arthritis Center 1945 Versailles St. Suite 101 Sarasota, FL 34239	Site 840060 Study Protocol EFC10832 7 enrolled subjects	March 29-31, 2016	NAI
Sanofi-Aventis U.S. LLC 500 Kendall Street Cambridge, MA 02142	Sponsor for: Study Protocol EFC11072 (Part B Subjects =1197 Study Protocol EFC10832 Subjects =546	May 11-27, 2016	Pending: Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. **Jacob Aelion, M.D./Study Protocol EFC11072 (Part B)/Site 840025**
   Jackson, TN 38305

The inspection was conducted from March 15 to 25, 2016. Under Study EFC11072 (Part B), a total of 27 subjects were screened and 15 subjects enrolled. Two patients withdrew consent and six subjects withdrew due to adverse events. Nine subjects completed the study. An audit of 15 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. However, a Form FDA 483 (Inspectional Observations) was issued at the conclusion of the inspection for another Study Protocol (i.e., not part of the DPARP consult, Protocol CHS-0214) during the inspection at Dr. Aelion's study site.

Since rheumatoid arthritis patients are essentially with immunosuppressed status on biologic therapy with sarilumab, development of serious infections such as opportunistic infections (e.g., fungal, tuberculous or herpes zoster infections, etc.) precludes them from further study participation. Per study protocol, the clinical study site was to inform sponsor immediately (i.e., within one working day).

There were inspectional discussion items for Protocol EFC11072 (Part B) related to adverse events, at the close out clinical site meeting with the P.I. Two subjects (Subject 202 on visit date October 5, 2011 and Subject 215 on visit date January 31, 2012) had herpes zoster infection and were treated with valacyclovir (Valtrex); however these patients were not discontinued immediately from the study. Subsequently, the sponsor asked the clinical site to discontinue these subjects from the study. These were considered non-critical regulatory deficiencies, and had no an impact on patient safety.

Notwithstanding the above non-critical regulatory observations at the site close out meeting, data submitted by this clinical site appear acceptable in support of this specific indication.

2. **Eric Lee, M.D./Study Protocol EFC10832/Site 840049**
   Upland, CA

The inspection was conducted from April 18-20, 2016. Under Study EFC10832, a total of 15 subjects were screened and 7 subjects enrolled. Two patients discontinued from the study after enrollment. Five patients completed the study. An audit of 15 screened subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Jeffrey Kaine, M.D./ Study Protocol EFC10832/ Site 840060
Sarasota, FL

The inspection was conducted from March 29 to 31, 2016. Under Study EFC10832, a total of 12 subjects were screened and seven enrolled. Four subjects discontinued early due to lack of efficacy. Three subjects completed the study. An audit of seven enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

4. Sanofi-Aventis U.S. LLC
Cambridge, MA

The inspection was conducted from May 11 to 27, 2016. This sponsor inspection was needed to ensure that there were no monitoring concerns for this biosimilar application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in GCP, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued at the end of the sponsor inspection. No monitoring problems were found during the sponsor inspection. Data submitted by this sponsor appear acceptable in support of the requested indication.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.
Review Division /Division Director/Badrul Chowdhury
Review Division/Associate Division Director/Sarah Yim
Review Division /Medical Team Leader/Janet Maynard
Review Division/Medical Officer/Suzette Peng
Review Division /Project Manager/Christine C. Ford
Review Division/MO/Anthony Orencia
OSI/Office Director/David Burrow (Acting)
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Janice Pohlman/Susan D. Thompson
OSI/DCCE/GCP Reviewer/Anthony Orencia
OSI/ GCP Program Analyst/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

ANTHONY J ORENCIA
07/18/2016

SUSAN D THOMPSON
07/18/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic

Date: April 12, 2016 **Update May 11, 2016

To: Christine Ford, Office of New Drugs, WO22-3306
christine.ford@fda.hhs.gov

Sandra Barnes, Office of New Drugs, WO22- 3312
sandra.barnes@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Christine Ford

Through: LT Viky Verna, Combination Product Branch Lead, Respiratory, ENT, General Hospital, Ophthalmic (REGO), DMQ, OC, CDRH, OMPT, WO66-3435

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.05.12 16:36:53 -04'00'

From: Jamie Kamon-Brancazio, REGO, DMQ, OC, CDRH

Applicant: Sanofi-Aventis U.S. LLC
55 Corporate Drive
Bridgewater, New Jersey 08807
FEI# 3003596612

Application # BLA-761037

Consult # ICC1600148

Product Name: Sarilumab 150 and 200 mg prefilled syringes

Pre-Approval Inspection: No

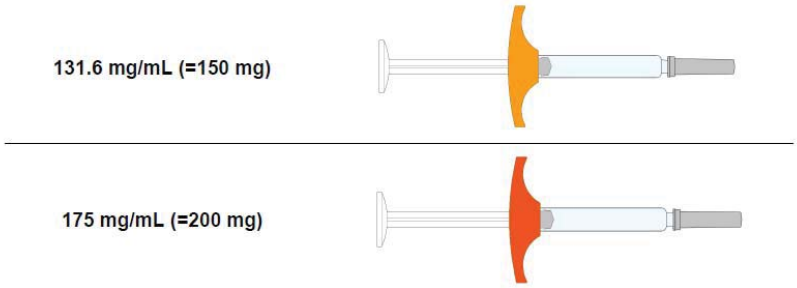
Documentation Review: Additional Information Required

Final Recommendation: **Approve**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA-761037.

PRODUCT DESCRIPTION

(b) (4) indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). The container closure system for sarilumab solution for injection is composed of the bulk prefilled syringe assembled with a plunger rod required to allow delivery of the PFS content and a finger flange to facilitate PFS grasping and handling.



REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Sanofi-Aventis U.S. LLC
   55 Corporate Drive
   Bridgewater, New Jersey 08807
   FEI# 3003596612

   Responsibility – Applicant

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on March 16-27 2015, comprised of drug coverage and was classified NAI.

Inspectional Recommendation:

An inspection is not required because:

- A recent inspection of the firm was acceptable.
- The firm does not perform manufacturing activities involving the the device constituent part. Therefore, the firm's compliance with 21 CFR Part 4 will be assured through the documentation review.

NOTE: As the applicant, the firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements.

2. Sanofi Winthrop Industrie

1051 Boulevard
Industriel
76580 LeTrait, France
FEI# 3003259844

Responsibility- Manufacture of bulk PFS and PFS, labeling and packaging the PFS, analytical release and stability testing, and post-approval stability studies

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on April 6-14 2015, comprised of drug coverage and was classified NAI.

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

3. Sanofi - Aventis U.S. LLC
   6244 Lemay Ferry Road
   Saint Louis, MO 63129
   FEI# 1000117606

   Responsibility – Secondary packaging and release for distribution of PFS.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on February 4-12, 2014 comprising of drug coverage and was classified NAI.

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20
Syringes are supplied sterile [redacted] (b) (4) and ready for use to Sanofi Winthrop Industrie (Le Trait). Syringe with staked needle and soft needle shield are controlled by the

supplier who delivers to Sanofi a certificate of conformity. The supplier is subject to regular audits as part of Sanofi Quality Assurance Program. Sanofi Winthrop Industrie performs all quality control testing of the syringes in addition to control of subcontractors. Sanofi has defined Quality Policies and Objectives. Sanofi has established the quality management system that comprises four elements, as described in the Quality Manual: Management Responsibility, Resource Management, Process Management and Measurement, Analysis and Improvement. The Quality manual is in place at Sanofi Winthrop Industrie, Le Trait. Sanofi's plan for quality is through the use of an integrated quality management system represented in the document hierarchy.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

Sanofi has procedures in place to control the design of the elements of the development activities and to ensure specified design requirements are met. The firm creates a Design Development Plan to describe all of the development and design activities, including planning, needs, and responsibilities. Design Input identifies user needs compiling information in reference to functional performance and design analysis to develop the design outputs. Design reviews are performed to assess the design result and are approved by Project Management and Quality.

Design verification activities are performed to document with objective evidences that the Design outputs meet the design input requirements, in order to evaluate and demonstrate conformance. For finished combination product, performance test are performed as part of the design verification program. Design validation activities are performed to document with objective evidences that the combination product complies with defined user needs and its intended use. Design Transfer activities ensure correct transfer of all documentation, methods, process and specifications to the industrial manufacturing site. Design changes are tracked into the DHF and managed according to a design change system to evaluate and control its implementation.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Sanofi has a purchased material management process and procedures in place which include:

- Evaluation and selection process for qualification of suppliers and materials

- Control over suppliers, including audits of the suppliers and sub-contractors

- Disposition of purchased materials

- Maintenance of associated quality records; acceptable suppliers

- Management policy for change notification and approval of changes in supplier or process components to determine whether such changes could affect the quality of the product.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The firm states, an internal SOP is in place at Sanofi Winthrop Industrie, Le Trait, which applies to all corrective/preventive actions resulting from:

- An investigation following an internal quality complaint or a deviation (including confirmed OOSs/OOTs),
- A laboratory anomaly (laboratory error),
- A return or batch recall,
- The analysis of a deviation recorded during a regulatory group or client inspection, self-inspection, or supplier and subcontractor audit,
- A trend analysis,
- An annual product or quality reviews,
- The implementation of a change with a measure of efficacy.

The firm did not provide a summary of analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

**Update- Jamie Kamon-Brancazio- 05/11/2016

Per the firm's response dated April 21, 2016, CAPA procedures are implemented by Quality departments. Corrective and preventative actions are initiated as a result of several factors ranging from internal events to complaints. Investigations are conducted to determine root cause and define appropriate actions to correct and prevent recurrence. The firm conducts regular progress review meetings to assess implementation, performance and effectiveness of the action.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

The facility has been designed as a multi-product facility (b) (4) [redacted]

Environmental controls are in place (b) (4) [redacted]

As part of its quality assurance program, Sanofi Winthrop Industrie performs the appropriate qualifications in terms of major equipment and areas. Qualification is carried out by conducting installation, operational and performance qualifications, individually or combined.

Production Flow

The manufacturing process for production of sarilumab solution for injection in bulk PFS at Sanofi, LeTrait consists of the following steps:

(b) (4) [redacted]

(b) (4)

Acceptance Activities

Internal SOP's are in place at Sanofi Winthrop Industrie, Le Trait that define the rules and responsibilities for managing the specifications of raw materials and packaging, including any incoming inspection and testing to ensure acceptance/receipt of conforming materials and packaging according to the current regulation. Final acceptance tests are described to ensure combination products meet established specifications prior to distribution. Component acceptance criteria comply with AQL. Pre-filled syringes are released by visual inspection and the container closure integrity is tested using a dye ingress method.

Documentation Review Recommendation

The firm's response to CDRH/OC deficiency was adequate.

RECOMMENDATION

The application for Sarilumab 150 and 200 mg prefilled syringes, BLA-761037, is approvable from the perspective of the applicable Quality System Requirements.

Jamie Kamon-brancazio -S

Digitally signed by Jamie Kamon-brancazio -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon-brancazio -S
Date: 2016.05.17 14:06:06 -04'00'

Jamie Kamon-Brancazio

Prepared: JKamon-Brancazio: 04/12/16- **Updated 5/11/16
Reviewed: VVerna: 04/14/2016

CTS No.: ICC1600148
BLA-761037

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:
Sanofi-Aventis U.S. LLC
55 Corporate Drive
Bridgewater, New Jersey 08807
FEI# 3003596612

CDRH recommends the inspection under the applicable Medical Device Regulations of Sanofi-Aventis U.S. LLC, located in Bridgewater, USA (FEI # 3003596612).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Jamie Kamon-Brancazio
CSO,
REGO
DMQ
Office of Compliance, WO66 RM 3427
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Francisco Vicenty
Chief
REGO
DMQ
Office of Compliance, WO66 RM 3426
Phone: 301-796- 2909

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

Inspectional Guidance

Firm to be inspected:

Sanofi Winthrop Industrie
1051 Boulevard
Industriel
76580 LeTrait, France
FEI# 3003259844

CDRH recommends the inspection under the applicable Medical Device Regulations of Sanofi Winthrop Industrie, located in Le Trait, France (FEI # 3003259844).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

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Inspectional Guidance

Firm to be inspected:

Sanofi - Aventis U.S. LLC
6244 Lemay Ferry Road
Saint Louis, MO 63129
FEI# 1000117606

CDRH recommends the inspection under the applicable Medical Device Regulations of Sanofi-Aventis U.S. LLC, located in Saint Louis, USA (FEI # 1000117606).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

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/s/

CHRISTINE H CHUNG

07/13/2016

uploading non-CDER consult review
Christine Ford (formerly Chung)

Food and Drug Administration
Center for Drug Evaluation and Research

CONSULTATION

DATE:	June 10, 2016
FROM:	Mary Roberts, M.D. Division of Metabolism and Endocrine Products (DMEP)
THROUGH:	Jim Smith, M.D., M.S. Deputy Director Division of Metabolism and Endocrine Products
TO:	Christine Ford, RPM Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
SUBJECT:	BLA 761037 Potential cardiovascular risk associated with lipid parameter changes seen with sarilumab (IL-6 receptor antibody)

I. Basis for Consult Request

Sarilumab is a human monoclonal antibody directed against the interleukin-6 (IL-6) receptor, currently under review for the treatment of patients with rheumatoid arthritis (RA). By blocking the IL-6 receptor, sarilumab disrupts IL-6 signaling and reduces markers of inflammation promoting favorable changes in measures of RA disease activity. However in clinical testing, treatment with sarilumab resulted in mild-to-moderate increases in lipid parameters (LDL-C, HDL-C, TG).

Of note, tocilizumab (ACTEMRA), an FDA approved IL-6 receptor monoclonal antibody for RA, exhibited similar changes in lipid parameters. As a condition of its approval, a cardiovascular outcome trial was required in the post-marketing setting. This CVOT is ongoing (NCT01331837). ACTEMRA labeling has a Warning & Precaution for Laboratory Parameters which includes lipid abnormalities and states:

Lipid Abnormalities

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1, 6.2)]*.

- Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy, then at approximately 24 week intervals.

- Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

The Division of Metabolism and Endocrinology Products has been consulted to opine and provide recommendations regarding the potential implications of the lipid changes observed with sarilumab treatment on cardiovascular risk.

II. Background

Sarilumab, a recombinant human immunoglobulin IgG1 monoclonal antibody targeting the interleukin 6 receptor, is currently under review for the treatment of moderately-to-severely active RA in patients who have had an inadequate response or intolerance to one or more disease modifying anti-rheumatic drugs (DMARDs). The proposed dose is 200 mg delivered subcutaneously every 2 weeks. Patients may reduce the dose to 150 mg every two weeks for management of neutropenia, thrombocytopenia, and elevated liver enzymes.

The clinical development program for sarilumab included studies using the 150 mg and 200 mg dose, sarilumab monotherapy, and sarilumab use in combination with methotrexate and other DMARDs. Two pivotal trials, EFC11072 Part B, Cohort 2 and EFC10832, were submitted to establish sarilumab's efficacy. Both were designed as randomized, double-blind, placebo-controlled add-on to either MTX or other DMARD therapy trials of 52 weeks and 24 weeks, respectively, with long-term extension periods. The shared co-primary endpoints for both trials were the proportion of American College of Rheumatology 20 responders at Week 24 and change in Health Assessment Questionnaire – Disability Index (HAQ-DI) score at Week 16 (EFC11072) or Week 12 (EFC10832). Please note, after Week 16 for EFC11072 and Week 12 EFC10832 patients with an inadequate response were "rescued" with open-label sarilumab 200 mg Q2W.

Study SFY13370 was a randomized, double-blind, double-dummy, 24-week study assessing the safety and tolerability of sarilumab and tocilizumab in patients with RA who were inadequate responders to or intolerant of TNF-α antagonists with the primary objective of assessing the safety of sarilumab and tocilizumab in the same study. Sarilumab was administered subcutaneously (SC) 150 mg Q2W or 200 mg Q2W. Tocilizumab was administered intravenously with an initial dose regimen of 4 mg/kg every 4 weeks (Q4W) with the option to increase the dose to 8 mg/kg Q4W at the Investigator's discretion.

Safety analyses were conducted using a pooled study strategy. Two of the safety pools included a placebo-controlled pool (Pool 1) and long-term safety pool (Pool 2). These are briefly described below.

The 52-week placebo-controlled population (Pool 1) includes patients from one Phase 2 study of 12 weeks duration and two Phase 3 efficacy studies (one of 24 weeks duration and the other of 52 weeks duration). In this population, 661 patients, 660 patients, and 661 patients received sarilumab 200 mg, sarilumab 150 mg, or placebo once every two weeks, respectively, in combination with DMARDs. This pool includes safety data collected during the double-blind treatment period. Once a patient entered the rescue

period, defined as the day when the first open-label dose of sarilumab was administered, data were no longer included in this pool.

The long-term safety population (Pool 2) of sarilumab on background DMARD therapy consisted of 2887 patients who received any dose of sarilumab. Of these, 2170 patients received sarilumab for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks. Duration of treatment for Pool 2 is up to 5 years. Due to study design there were multiple dosing regimens summarized in 3 groups: 150 mg sarilumab (initial) + DMARD, 200 mg sarilumab (initial) + DMARD, and Any sarilumab dose + DMARD. Note that by design, the duration of exposure for patients initiating dosing with 150 mg Q2W is less than that for patients who initiated dosing at 200 mg Q2W.

In the Statistical Analysis Plan, the three treatment groups in Pool 2 are described as follows:

- Sarilumab 150 mg Q2W initial dose + DMARD: includes patients whose initial dose of sarilumab was 150 mg Q2W, and includes data up to the dose modification for patients who were rescued or enrolled in LTS11210, the end of study or data cut-off date
- Sarilumab 200 mg Q2W initial dose + DMARD: includes patients whose initial dose of sarilumab was 200 mg Q2W, and includes data up to dose modification, the end of study or data cut-off date.
- Any sarilumab dose + DMARD: includes patients on any dose of sarilumab, and includes data from time of first sarilumab dose to the end of the study or data cut-off date

Relevant exclusion criteria included patients with severe uncontrolled hypercholesterolemia (>350 mg/dL), or hypertriglyceridemia (>500 mg/dL) at screening or baseline or patients with new treatment or dose adjustment of lipid-modifying therapy within 6 weeks prior to randomization. Management of lipid levels and reporting of associated AEs was left to Investigator discretion, with advice to follow local lipid treatment guidelines.

III. Effect on Lipid levels

Placebo-controlled pool

At Baseline in Pool 1 (placebo-controlled pool), the mean values of LDL-C and HDL-C were approximately 109 mg/dL and 59 mg/dL, respectively; median TG level was approximately 115 mg/dL. Concomitant lipid-modifying therapy (not further defined) was reported for 10% of patients.

Reviewer comment: It is not unexpected to note normal levels of lipids in patients with RA as reflected in the baseline values in the patients comprising Pool 1.[1] *However, these*

[1] Liao KP et al. Lipid and lipoprotein levels and trends in rheumatoid arthritis compared with the general population. Arthritis Care Res. 2013;65:2046-50.

values may be misleading for use in assessing cardiovascular risk as evidence suggests a non-linear relationship between total cholesterol and LDL-C and degree of cardiovascular risk, known as the lipid paradox.[2] In a retrospective cohort study of 651 patients with RA, there was a U-shaped relationship observed, where patients with lower total cholesterol and LDL-C levels had higher CV risk. Inflammation is thought to be underlying these altered lipid profiles, although the exact mechanism(s) is unknown.[3]

Serum lipids, total cholesterol, HDL-C, LDL-C, and triglycerides increased more in patients treated with 150 mg and 200 mg of sarilumab+DMARD every 2 weeks compared with patients treated with placebo + DMARD (Table 1). The individual study results were consistent with the pooled results presented below.

The increases were evident at Week 4 (the first time lipid levels checked post-dose). At Week 4, the mean percent increase in LDL-C for 200 mg Q2W sarilumab-treated patients was 16% (15.8 mg/dL), which was an estimated 14.5% difference from placebo. These values in general remained elevated throughout the treatment period and were similar between sarilumab doses (Figure 1, Figure 2, Figure 3). Please note the duration of treatment for Pool 1 is up to 52 weeks; however two of the 3 studies comprising this pool had treatment duration of 12 and 24 weeks, which is reflected in the reduced number of patients with available measurements at the 52 week time point.

Table 1 Percent Change from Baseline in LDL-C, HDL-C, and TG (Pool 1)

	Placebo +DMARD N=661	**150 mg Q2W +DMARD N=660**	**200 mg Q2W +DMARD N=661**
LDL-C (mg/dL)			
Baseline			
n	660	660	661
Mean (SD)	109 (31)	108 (32)	109 (31)
Week 4 percent change from baseline			
n	645	636	634
Mean% change	1.7	14.9	16.2
Mean difference vs placebo	--	13.2	14.5
95% CI	--	(10.5, 16.0)	(11.7, 17.3)
Week 12 percent change from baseline			
n	623	601	604
Mean% change	2.1	18.1	17.8
Mean difference vs placebo	--	16.0	15.7
95% CI	--	(12.9, 19.1)	(12.6, 18.8)
Week 52 percent change from baseline			
n	206	284	277
Mean% change	3.1	17.1	17.1
Mean difference vs placebo	-	14.0	14.1
95% CI	-	(9.3, 18.7)	(9.3, 18.8)
HDL-C (mg/dL)			

[2] Myasoedova E et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482-7.
[3] Robertson J et al. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. Nat. Rev. Rheumatol. 2013;9:513-23.

	Placebo +DMARD N=661	150 mg Q2W +DMARD N=660	200 mg Q2W +DMARD N=661
Baseline			
n	661	660	661
Mean (SD)	58.9 (16.7)	59.7 (16.7)	58.9 (16.2)
Week 4 percent change from baseline			
n	649	648	641
Mean% change	1.9	6.3	6.5
Mean difference vs placebo	--	4.4	4.6
95% CI	--	(2.4, 6.3)	(2.6, 6.5)
Week 12 percent change from baseline			
n	625	610	619
Mean% change	3.3	6.1	7.1
Mean difference vs placebo	--	2.8	3.9
95% CI	--	(0.7, 4.9)	(1.8, 6.0)
Week 52 percent change from baseline			
n	206	292	278
Mean% change	1.0	3.5	2.4
Mean difference vs placebo	--	2.5	1.4
95% CI	--	(-1.2, 6.2)	(-2.3, 5.1)
Triglyceride (mg/dL)			
Baseline			
n	661	660	661
Mean	134 (70)	133 (72)	129 (62)
Median	114	118	115
Week 4 percent change from baseline			
n	650	648	641
Mean% change	2.0	19.1	25.5
Mean difference vs placebo	--	17.1	23.5
95% CI	--	(12.6, 21.5)	(19.0, 27.9)
Median % change	-1.2	10.2	19.4
Week 12 percent change from baseline			
n	626	611	619
Mean% change	2.3	20.3	25.3
Mean difference vs placebo	--	18	23
95% CI	--	(13.1, 22.9)	(18.2, 27.9)
Median % change	-3.8	10.7	17.2
Week 52 percent change from baseline			
n	206	292	279
Mean% change	3.5	29.3	30.6
Mean difference vs placebo	--	25.8	27.1
95% CI	--	(16.3, 35.2)	(17.5, 36.7)
Median % change	0	14.7	17.9

Source: BLA 761037 ISS Appendix 1.5.1.262

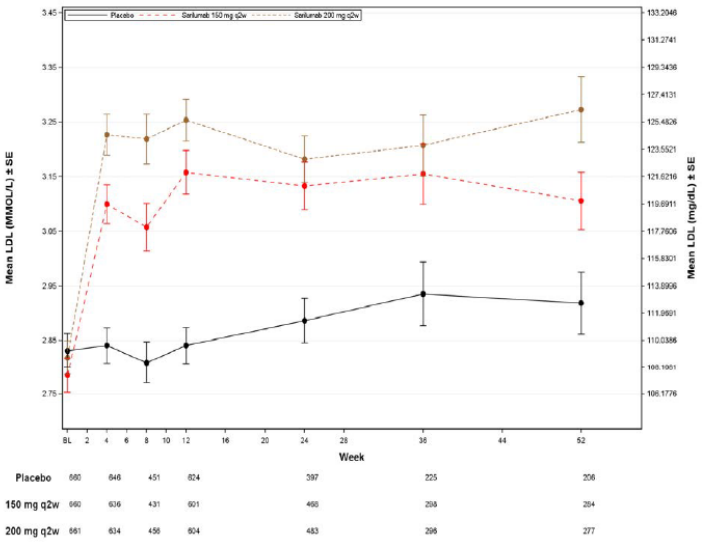

Figure 1. Mean LDL-C across visits during the entire TEAE period – Placebo-controlled safety population (Pool 1)
Source: BLA 761037, ISS, Figure 24

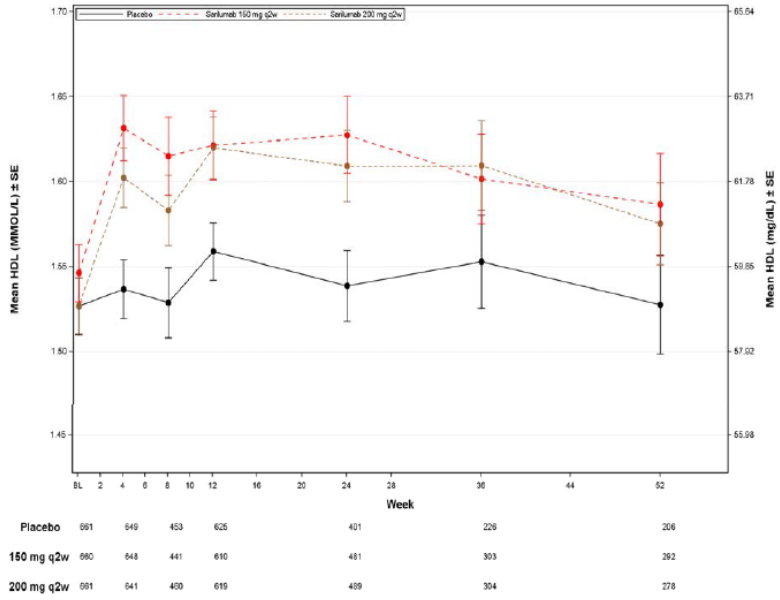

Figure 2. Mean HDL-C across visits during the entire TEAE period – Placebo-controlled safety population (Pool 1)
Source: BLA 761037, ISS, Figure 25

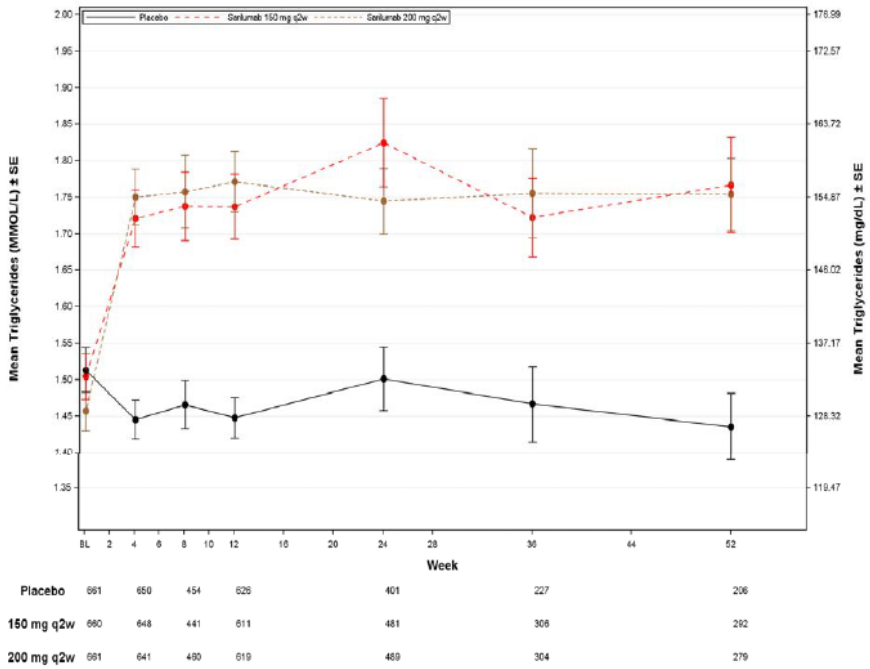

Figure 3. Mean triglyceride across visits during the entire TEAE period – Placebo-controlled safety population (Pool 1)
Source: BLA 761037, ISS, Figure 26

Reviewer comment: Due to differences in study duration, the numbers of patients contributing to lipid measurements falls considerably after Week 12, leading to greater degree of uncertainty in the exact magnitude of lipid elevation at later time points, however the overall trend in lipid elevations with sarilumab appears to be consistent and stable.

The applicant analyzed shifts in lipid values by NCEP ATP III LDL classification categories using baseline and average post-baseline LDL values. Consistent with the mean changes, a higher proportion of sarilumab-treated patients experienced a shift to a higher LDL-C category compared to placebo-treated patients in each baseline LDL-C category. For instance, of those with baseline LDL-C less than 100 mg/dL, 81% of patients treated with placebo had average post-baseline LDL values which remained within this category, versus 59% and 51% of patients in treated with 150 mg and 200 mg sarilumab, respectively. Within the <100 mg/dL LDL baseline group, a smaller proportion of placebo-treated patients (1.5%) had higher average post-baseline LDL values in the 130-160 mg/dL category compared 7.1% of patients in the 150 mg sarilumab group and 6.6% in the 200 mg sarilumab group.

Table 2. LDL-C Number of patients by NCEP ATPIII LDL classification according to baseline status based on average of post-baseline values during the entire TEAE period - Placebo-controlled safety population (Pool 1)

Laboratory parameter Baseline Postbaseline n/N1 (%)	Placebo + DMARD (N=661)	Sarilumab 150 mg q2w + DMARD (N=660)	Sarilumab 200 mg q2w + DMARD (N=661)
LDL			
Total[a]			
< 100 mg/dL	255/660 (38.6%)	181/655 (27.6%)	152/655 (23.2%)
100 - < 130 mg/dL	240/660 (36.4%)	237/655 (36.2%)	232/655 (35.4%)
130 - < 160 mg/dL	133/660 (20.2%)	159/655 (24.3%)	167/655 (25.5%)
160 - < 190 mg/dL	27/660 (4.1%)	63/655 (9.6%)	80/655 (12.2%)
≥190 mg/dL	5/660 (0.8%)	15/655 (2.3%)	24/655 (3.7%)
Missing			
< 100 mg/dL	1/1 (100%)	0/0	0/0
100 - < 130 mg/dL	0/1	0/0	0/0
130 - < 160 mg/dL	0/1	0/0	0/0
160 - < 190 mg/dL	0/1	0/0	0/0
≥190 mg/dL	0/1	0/0	0/0
< 100 mg/dL			
< 100 mg/dL	212/263 (80.6%)	164/280 (58.6%)	132/259 (51.0%)
100 - < 130 mg/dL	47/263 (17.9%)	95/280 (33.9%)	108/259 (41.7%)
130 - < 160 mg/dL	4/263 (1.5%)	20/280 (7.1%)	17/259 (6.6%)
160 - < 190 mg/dL	0/263	1/280 (0.4%)	2/259 (0.8%)
≥190 mg/dL	0/263	0/280	0/259
100 - < 130 mg/dL			
< 100 mg/dL	40/235 (17.0%)	16/223 (7.2%)	18/249 (7.2%)
100 - < 130 mg/dL	156/235 (66.4%)	112/223 (50.2%)	109/249 (43.8%)
130 - < 160 mg/dL	35/235 (14.9%)	78/223 (35.0%)	95/249 (38.2%)
160 - < 190 mg/dL	4/235 (1.7%)	15/223 (6.7%)	26/249 (10.4%)
≥190 mg/dL	0/235	2/223 (0.9%)	1/249 (0.4%)
130 - < 160 mg/dL			
< 100 mg/dL	2/117 (1.7%)	0/110	2/104 (1.9%)
100 - < 130 mg/dL	34/117 (29.1%)	28/110 (25.5%)	12/104 (11.5%)
130 - < 160 mg/dL	71/117 (60.7%)	50/110 (45.5%)	48/104 (46.2%)
160 - < 190 mg/dL	10/117 (8.5%)	29/110 (26.4%)	35/104 (33.7%)
≥190 mg/dL	0/117	3/110 (2.7%)	7/104 (6.7%)
160 - < 190 mg/dL			
< 100 mg/dL	0/38	1/34 (2.9%)	0/38
100 - < 130 mg/dL	3/38 (7.9%)	2/34 (5.9%)	2/38 (5.3%)
130 - < 160 mg/dL	21/38 (55.3%)	10/34 (29.4%)	6/38 (15.8%)
160 - < 190 mg/dL	12/38 (31.6%)	14/34 (41.2%)	17/38 (44.7%)
≥190 mg/dL	2/38 (5.3%)	7/34 (20.6%)	13/38 (34.2%)

Laboratory parameter Baseline Postbaseline n/N1 (%)	Placebo + DMARD (N=661)	Sarilumab 150 mg q2w + DMARD (N=660)	Sarilumab 200 mg q2w + DMARD (N=661)
≥190 mg/dL			
< 100 mg/dL	0/6	0/8	0/5
100 - < 130 mg/dL	0/6	0/8	1/5 (20.0%)
130 - < 160 mg/dL	2/6 (33.3%)	1/8 (12.5%)	1/5 (20.0%)
160 - < 190 mg/dL	1/6 (16.7%)	4/8 (50.0%)	0/5
≥190 mg/dL	3/6 (50.0%)	3/8 (37.5%)	3/5 (60.0%)

a Regardless of baseline status.

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.

Average of all post-baseline measurements for each patient is presented by baseline status.

Source: BLA 761037, ISS, Table 90

Statin initiation was also higher in the patient population treated with sarilumab (2.4%) versus placebo (0.5%) in the placebo-controlled safety pool (Pool 1). We were unable to locate data regarding lipid changes among those taking statins at baseline, or among those who initiated statins during the trials.

There was a higher proportion of patients in Pool 1 with TG ≥496 mg/dL treated with sarilumab (4.3% in 150 mg group; 2.3% in 200 mg group) versus placebo (0.3%). There were no lipid-related SAEs in Pool 1. In the long-term safety database (Pool 2), there was 1 elevated lipid reported as an SAE, for an asymptomatic TG level of 1021 mg/dL on Day 673 in a sarilumab-treated patient with a history of hypertriglyceridemia who was not taking the appropriate dosage of gemfibrozil prescribed (taking 500 mg/day instead of 1500 mg/day). On Day 695, after resuming correct dosage of 1500 mg per day of gemfibrozil, the patient's TG was 214 mg/dL.

Active comparator controlled study

SFY13370 was a randomized, double-blind, double-dummy, 24-week study designed with the primary objective of evaluating safety of sarilumab and tocilizumab, the FDA-approved IL-6 receptor mAb, in patients with RA with an inadequate response to TNF antagonists. A total of 202 patients with RA on background DMARD therapy were randomized 1:1:2 to receive sarilumab 150 mg Q2W, sarilumab 200 mg Q2W, or IV infusion of tociluzumab every 4 weeks starting at 4 mg/kg with uptitration to 8 mg/kg if needed. Lipid lowering drugs were permitted if dosing was stable for ≥6 weeks before screening. If, during the study, patients were found to have significant increase in cholesterol levels, then cholesterol lowering therapy per NCEP/ATP III or local guidelines should have been initiated or the dose of concomitant lipid lowering drugs should have been adjusted.

The demographic and baseline characteristics were well matched across treatment groups. The mean age was 51.8 years, the majority of patients were female (80%) and White (93%). Approximately 29% were obese (BMI ≥30 kg/m^2), one-third reported hypertension, and 13% were on statin therapy at baseline. Average LDL-C at baseline was approximately 110 mg/dL and median TG level was 108 mg/dL.

As shown in the figure below, there were similar increases in mean LDL-C in the sarilumab and tocilizumab treated groups. At Week 24, the absolute mean change from baseline was 18.0 mg/dL, 17.9 mg/dL, and 16.9 mg/dL in the tocilizumab Q4W, sarilumab 150 mg Q2W, and sarilumab 200 mg Q2W groups, respectively.

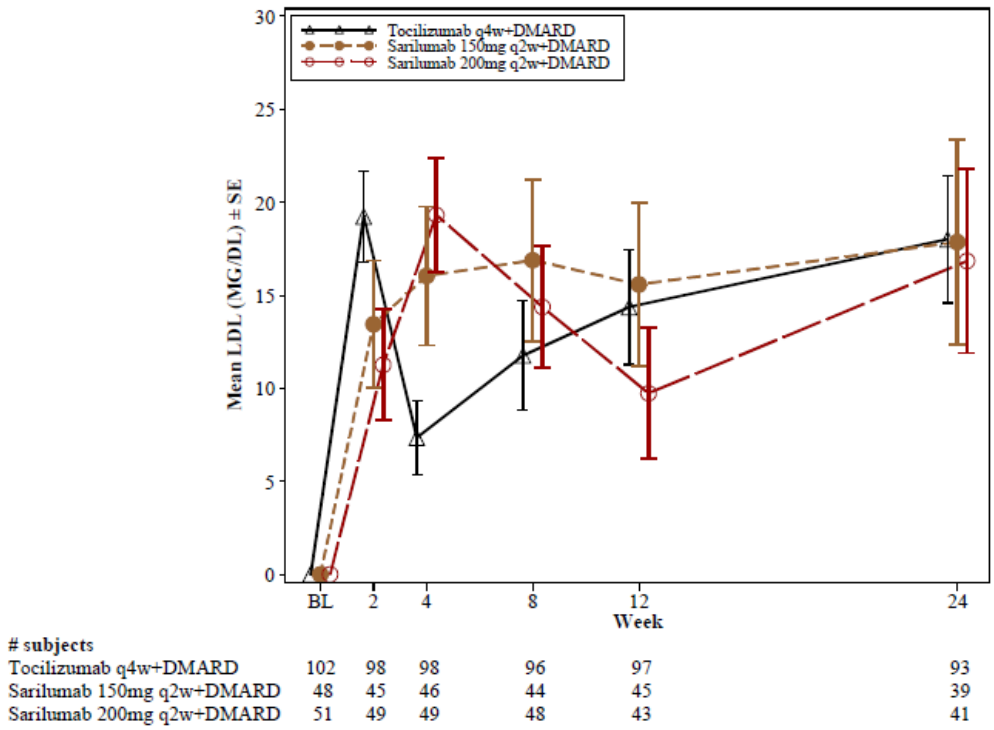

Figure 4. Mean change from baseline in LDL-C at each visit – Safety population
Source: SFY13370 Appendix 16.2.8.1.63

Increases in total cholesterol, HDL-C, and TG were also observed from baseline in both the tocilizumab and sarilumab treated groups and were similar in magnitude of elevation (Table 3).

Table 3. Percent Change from Baseline in LDL-C, HDL-C, and TG (Study SFY13370)

	Tocilizumab Q4W +DMARD N=102	Sarilumab 150 mg Q2W +DMARD N=49	Sarilumab 200 mg Q2W +DMARD N=51
LDL-C (mg/dL)			
Baseline			
n	102	48	51
Mean (SD)	112 (38)	110 (32)	109 (24)
Week 12 percent change from baseline			
n	97	45	43
Mean% change	16.2	16.2	11.5
Mean difference vs tocilizumab[b]	--	0.08	-4.7
95% CI[b]	--	(-8.8, 9.0)	(-13.7, 4.3)
Week 24 percent change from baseline			
n	93	39	41
Mean% change	21.3	18.2	17.1
Mean difference vs tocilizumab[b]	--	-3.1	-4.1
95% CI[b]	--	(-14.2, 8.0)	(-15.0, 6.7)

	Tocilizumab Q4W +DMARD N=102	Sarilumab	
		150 mg Q2W +DMARD N=49	200 mg Q2W +DMARD N=51
Last on-treatment value[a]			
n	101	47	51
Mean% change	16.2	16.6	16.1
Mean difference vs tocilizumab[b]	--	0.38	-0.04
95% CI[b]	--	(-9.0, 9.8)	(-9.1, 9.1)
HDL-C (mg/dL)			
Baseline			
n	102	49	51
Mean (SD)	61.2 (15.1)	62.6 (19.1)	64.5 (19.6)
Week 12 percent change from baseline			
n	99	45	43
Mean% change	10.9	8.5	7.0
Mean difference vs tocilizumab[b]	--	-2.4	-3.9
95% CI[b]	--	(-9.7,4.9)	(-11.3, 3.5)
Week 24 percent change from baseline			
n	96	40	41
Mean% change	10.7	11.9	6.3
Mean difference vs tocilizumab[b]	--	1.2	-4.4
95% CI[b]	--	(-7.3, 9.7)	(-12.8, 4.0)
Last on-treatment value[a]			
n	101	48	51
Mean% change	11.0	8.2	8.0
Mean difference vs tocilizumab[b]	--	-2.8	-3.0
95% CI[b]	--	(-10.5, 4.9)	(-10.6, 4.5)
Triglyceride (mg/dL)			
Baseline			
n	102	49	51
Mean	117 (50)	145 (101)	120 (59)
Median	109	109	108
Week 12 percent change from baseline			
n	99	45	43
Mean% change	14.8	17.2	19.0
Mean difference vs tocilizumab[b]	--	2.4	4.2
95% CI[b]	--	(-15.0, 19.7)	(-13.4, 21.8)
Median % change	6.1	3.3	4.6
Week 24 percent change from baseline			
n	96	40	41
Mean% change	22.0	13.2	22.2
Mean difference vs tocilizumab[b]	--	-8.7	0.15
95% CI[b]	--	(-28.0, 10.5)	(-18.9, 19.2)
Median % change	11.4	11.6	13.5
Last on-treatment value[a]			
n	101	48	51
Mean% change	13.8	24.6	15.3
Mean difference vs tocilizumab[b]	--	10.8	1.6
95% CI[b]	--	(-7.2, 28.8)	(-16.1, 19.2)
Median % change	4.8	9.9	3.3

Source: SFY 13370 Appendix 16.2.8.1.100

a Last on-treatment value is defined as the last value collected during the treatment period.

b Estimated using an analysis of variance model with treatment as the factor

Based on mean post-baseline LDL values, the majority of patients remained within their baseline LDL-C category. There was a slightly higher proportion of sarilumab-treated patients with baseline values <100 mg/dL that shifted to a higher LDL-C category compared to tocilizumab-treated patients, however the numbers contributing to each category were small and therefore the significance of these relatively small differences is unknown.

Table 2 - LDL - Number of patients with different post-baseline value (based on mean post-baseline value for each patient) according to baseline status during the TEAE period - Safety population (separating tocilizumab subsets)

	Tocilizumab			Sarilumab	
Laboratory parameter Baseline Postbaseline n/N1 (%)	4 mg/kg q4w + DMARD (N=40)	4/8 mg/kg q4w + DMARD (N=39)	q4w + DMARD (N=102)	150mg q2w + DMARD (N=49)	200mg q2w + DMARD (N=51)
LDL					
Total [a]					
< 100 mg/dL	14/39 (35.9%)	8/39 (20.5%)	29/101 (28.7%)	12/47 (25.5%)	9/51 (17.6%)
100 - < 130 mg/dL	11/39 (28.2%)	7/39 (17.9%)	25/101 (24.8%)	13/47 (27.7%)	24/51 (47.1%)
130 - < 160 mg/dL	9/39 (23.1%)	17/39 (43.6%)	31/101 (30.7%)	15/47 (31.9%)	16/51 (31.4%)
160 - < 190 mg/dL	2/39 (5.1%)	4/39 (10.3%)	9/101 (8.9%)	6/47 (12.8%)	1/51 (2.0%)
≥190 mg/dL	3/39 (7.7%)	3/39 (7.7%)	7/101 (6.9%)	1/47 (2.1%)	1/51 (2.0%)
Missing					
< 100 mg/dL	0/0	0/0	0/0	0/0	0/0
100 - < 130 mg/dL	0/0	0/0	0/0	0/0	0/0
130 - < 160 mg/dL	0/0	0/0	0/0	0/0	0/0
160 - < 190 mg/dL	0/0	0/0	0/0	0/0	0/0
≥190 mg/dL	0/0	0/0	0/0	0/0	0/0
< 100 mg/dL					
< 100 mg/dL	14/18 (77.8%)	8/12 (66.7%)	27/38 (71.1%)	11/19 (57.9%)	8/17 (47.1%)
100 - < 130 mg/dL	4/18 (22.2%)	2/12 (16.7%)	8/38 (21.1%)	5/19 (26.3%)	8/17 (47.1%)
130 - < 160 mg/dL	0/18	2/12 (16.7%)	3/38 (7.9%)	3/19 (15.8%)	1/17 (5.9%)
160 - < 190 mg/dL	0/18	0/12	0/38	0/19	0/17
≥190 mg/dL	0/18	0/12	0/38	0/19	0/17
100 - < 130 mg/dL					
< 100 mg/dL	0/8	0/15	2/35 (5.7%)	1/14 (7.1%)	1/24 (4.2%)
100 - < 130 mg/dL	7/8 (87.5%)	5/15 (33.3%)	15/35 (42.9%)	6/14 (42.9%)	13/24 (54.2%)
130 - < 160 mg/dL	1/8 (12.5%)	8/15 (53.3%)	13/35 (37.1%)	6/14 (42.9%)	9/24 (37.5%)
160 - < 190 mg/dL	0/8	2/15 (13.3%)	5/35 (14.3%)	1/14 (7.1%)	1/24 (4.2%)
≥190 mg/dL	0/8	0/15	0/35	0/14	0/24
130 - < 160 mg/dL					
< 100 mg/dL	0/7	0/8	0/18	0/10	0/9
100 - < 130 mg/dL	0/7	0/8	2/18 (11.1%)	1/10 (10.0%)	3/9 (33.3%)
130 - < 160 mg/dL	7/7 (100%)	4/8 (50.0%)	11/18 (61.1%)	5/10 (50.0%)	6/9 (66.7%)
160 - < 190 mg/dL	0/7	1/8 (12.5%)	1/18 (5.6%)	3/10 (30.0%)	0/9
≥190 mg/dL	0/7	3/8 (37.5%)	4/18 (22.2%)	1/10 (10.0%)	0/9
160 - < 190 mg/dL					
< 100 mg/dL	0/3	0/3	0/6	0/4	0/1
100 - < 130 mg/dL	0/3	0/3	0/6	1/4 (25.0%)	0/1
130 - < 160 mg/dL	1/3 (33.3%)	2/3 (66.7%)	3/6 (50.0%)	1/4 (25.0%)	0/1
160 - < 190 mg/dL	1/3 (33.3%)	1/3 (33.3%)	2/6 (33.3%)	2/4 (50.0%)	0/1
≥190 mg/dL	1/3 (33.3%)	0/3	1/6 (16.7%)	0/4	1/1 (100%)
≥190 mg/dL					
< 100 mg/dL	0/3	0/1	0/4	0/0	0/0
100 - < 130 mg/dL	0/3	0/1	0/4	0/0	0/0
130 - < 160 mg/dL	0/3	1/1 (100%)	1/4 (25.0%)	0/0	0/0
160 - < 190 mg/dL	1/3 (33.3%)	0/1	1/4 (25.0%)	0/0	0/0
≥190 mg/dL	2/3 (66.7%)	0/1	2/4 (50.0%)	0/0	0/0

PCSA: Potentially clinically significant abnormalities.

Note: The number (n) represents the subset of the total number of patients who met the criterion in question at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients for the treatment group who had that parameter assessed post-baseline.

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Source: BLA 761037, SFY 13370, Appendix 15.3.4, Table 2

Seven (6.9%) patients in the tocilizumab group, 2 (4.1%) in the 150 mg Q2W sarilumab group, and 2 (3.9%) in the 200 mg Q2W sarilumab group initiated treatment with statins. Of 26 (12.9%) patients on baseline statin, no patients in the sarilumab group discontinued or modified the statin dose. One tocilizumab-treated patient discontinued statin use.

There were no events adjudicated as MACE in the sarilumab treated groups. One event (septic shock) was adjudicated as CV death and occurred in the tocilizumab group.

IV. Effect on CRP

Pivotal Phase 3 studies

Through its blockade of IL-6R, sarilumab is expected to lower CRP. CRP was assessed as a component of the primary endpoint, the ACR response score, at Week 24. In the two Phase 3 trials for determining efficacy, the baseline mean CRP was approximately 22 mg/L and 27 mg/L in EFC11072 Part B, Cohort 2 and EFC10832, respectively. In both studies there was a statistically significant decrease in mean CRP with either 150 mg or 200 mg sarilumab compared to placebo (Table 4).

Table 4. Mean change from baseline in components of ACR score at Week 24 in 2 Phase 3 studies

	EFC11072 Part B, Cohort 2						EFC10832					
	Placebo + MTX (N=398)		Sarilumab 150 mg q2w + MTX (N=400)		Sarilumab 200 mg q2w + MTX (N=399)		Placebo + DMARD (N=181)		Sarilumab 150 mg q2w + DMARD (N=181)		Sarilumab 200 mg q2w + DMARD (N=184)	
Component (mean)	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
CRP												
Mean(SD)	20.46(23.01)	17.26 (22.31)	22.53(23.09)	8.85 (23.46)	22.19(23.77)	3.82 (14.21)	26.02(25.20)	19.83 (22.20)	23.60(23.44)	8.76 (14.86)	30.77 (28.35)	3.74 (8.97)
Mean change from baseline		-0.14(21.52)		-13.63 (29.49)		-18.04 (24.93)		-5.21(25.67)		-13.11(20.35)		-29.06 (31.29)
LS mean difference vs. placebo (95% CI) [a]				-12.538 (-15.863,-9.212)		-16.903 (-20.218,-13.588)				-11.642 (15.651,-7.6344)		-19.673 (-23.636,-15.7099
p-value vs. placebo [a]				<0.0001		<0.0001				<0.0001		<0.0001

ANCOVA=analysis of covariance; CI=confidence interval; DMARD= disease-modifying antirheumatic drugs; LS=least squares; MMRM=mixed model for repeated measures; MTX=methotrexate; Number = Number of patients with assessment at both baseline and Week 24; SD=standard deviation; TNF=tumor necrosis factor, VAS=visual analogic scale.

Source: 5.3.5.1 Studies EFC11072 Part B appendix 16-2-6-eff-response-data [16.2.6.1.9] to [16.2.6.1.14] and [16.2.6.1.2.3] and EFC10832 appendix 16-2-6-eff-response-data [16.2.6.5] to [16.2.6.10] and [16.2.6.2.3].

a Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use/number of previous anti TNFs, region, visit, and treatment by visit interaction. All assessments are set to missing from the time a patient receives rescue medication or discontinues study medication early. Missing measurements are not imputed.

Source: BLA 761037, Summary of Clinical Efficacy, Adapted Table 19

V. Major Adverse Cardiovascular Events

All deaths, serious cardiovascular adverse events, and any non-serious adverse event requiring a cardiovascular procedure were adjudicated by an external cardiovascular adjudication committee (CAC). Two composite MACE endpoints were defined: MACE (primary) comprised CV Death, Myocardial Infarction, Stroke, Hospitalization for unstable angina (UA), or Hospitalization for transient ischemic attack (TIA); MACE (narrow) comprised CV Death, MI, or Stroke.

From the placebo-controlled studies, EFC11072 Part A and B and EFC 10832 there were a total of 5 events adjudicated as MACE (1 occurred in study EFC10832 and 4 in study EFC 11072 Part B).

*Reviewer comment: Please note that the ISS only reports 4 events as MACE. There are no events described in the ISS as occurring in the placebo group. The CSR for EFC 11072 Part B, reports a treatment emergent MACE event in a placebo-treated subject (*EFC 11072-032-001-203). *This is also reflected in the ADCE.xpt database for this study. In the ISS, ADCE.xpt database, this subject's MACE is flagged as a post-study event and appears to not be included in the ISS analysis of MACE. We would*

recommend confirmation of the timing of this event and the appropriateness of its inclusion in analyses of MACE.

In study EFC10832, which was 24 weeks in duration, a total of 8 adverse events were adjudicated by the CAC, of which 1 was adjudicated as stroke occurring in the sarilumab 200 mg Q2W group.

In study EFC11072 Part B, which was 52 weeks in duration, a total of 21 adverse events were adjudicated by the CAC, of which 4 were adjudicated as MACE. Of the 4 events (1 was in the placebo group, 2 were in the sarilumab 150 mg Q2W group, and 1 was in the sarilumab 200 mg Q2W group) that were adjudicated as MACE, 2 events were adjudicated as cardiovascular deaths and 2 events were adjudicated as non-fatal stroke.

Table 5. Number (%) of patients with events adjudicated by CAC as MACE by study

	EFC11072 Part B			**EFC10832**		
	Placebo + MTX N=427 n (%)	**150 mg Q2W +MTX N=431 n (%)**	**200 mg Q2W +MTX N=424 n (%)**	**Placebo +DMARD N=181 n (%)**	**150 mg Q2W +DMARD N=181 n (%)**	**200 mg Q2W +DMARD N=184 n (%)**
MACE (primary)	1 (0.2)	2 (0.5)	1 (0.2)	0	0	1 (0.5%)
MACE (narrow)	1 (0.2)	2 (0.5)	1 (0.2)	0	0	1 (0.5%)
CV Death	0	1 (0.2)	1 (0.2)	0	0	0
Myocardial infarction	0	0	0	0	0	0
Heart Failure	0	0	0	0	0	0
Stroke	0	0	0	0	0	0
Procedure-related death	0	0	0	0	0	0
Other CV causes	0	1 (0.2)	1 (0.2)	0	0	0
Undetermined cause of death	0	0	0	0	0	0
MI (non-fatal)	0	0	0	0	0	0
Hospitalization for unstable angina (non-fatal)	0	0	0	0	0	0
Heart failure (non-fatal)	0	0	0	0	0	0
Stroke (non-fatal)	1 (0.2)	1 (0.2)	0	0	0	1 (0.5%)
Hospitalization for transient ischemic attack (non-fatal)	0	0	0	0	0	0

Source: CSR EFC110072 Part B Table 46; CSR EFC10832 Table 47

Brief narratives of CAC adjudicated MACE

- **Non-fatal stroke (EFC 11072-032-001-203/placebo)** 58-year-old man in the placebo group experienced ischemic stroke secondary to endocarditis, 64 days after the last dose of the IMP.
- **CV death (EFC 11072-643-008-215/sarilumab 150 mg Q2W)** 56-year-old woman on sarilumab 150 mg Q2W. On Day 15, patient's labs were remarkable for neutropenia and thrombocytopenia. The patient received her second dose of sarilumab on Day 15 before results of lab tests were known. On Day 18, the patient was asked to return to the clinic and discontinue sarilumab. On Day 21, 6 days after last dose of sarilumab, the patient died suddenly. Autopsy report

diagnosed chronic ischemic heart disease, abnormal myocardial blood flow, pulmonary edema, and cerebral edema. There were no signs of pulmonary embolism. The event of cardiogenic pulmonary edema was adjudicated by the Cardiovascular Adjudication Committee (CAC) as death (cardiovascular death). [CAC comment: Possible myocardial infarction or pulmonary embolism -autopsy showing cardiogenic pulmonary edema]. This patient was not on a statin.

- **CV death (EFC 11072-032-009-212/sarilumab 200 mg Q2W)** 59-year-old man with medical history of hypertension, obesity, and smoking, died due to a suspected cerebrovascular accident on Day 107. [CAC comment: Quite confusing report. Suggestion of stroke (but no evidence). Could be pulmonary embolism or heart failure. CV death most probable due to rapid progression until respiratory and cardiac arrest].
- **Non-fatal stroke (EFC 11072-152-001-211/sarilumab 150 mg Q2W**) 49-year-old man in the sarilumab 150 mg q2w group, with medical history of chronic obstructive pulmonary disease, experienced a stroke, mesenteric ischemia, and renal and splenic infarcts secondary to multiple emboli from an aortic thrombus on Day 140.
- **Non-fatal stroke (EFC 10832/sarilumab 200 mg Q2W)** 67-year-old female presented with severe weakness and communication difficulty and was diagnosed with an ischemic stroke, non-STEMI myocardial infarction and non-infectious endocarditis after 150 days of treatment (11 administrations) of 200 mg sarilumab Q2W. During workups in this hospitalization, based on pre-operative echocardiographic findings, the initial diagnosis was mitral valve tumor. Following thoracotomy and biopsy of the valvular mass, the histopathology findings were consistent with non-infectious endocarditis (probably growth related to RA) that most likely contributed to the multiple cerebral ischemic infarcts. The CAC adjudicated the ischemic stroke as a stroke and did not adjudicate the non-STEMI myocardial infarction as a myocardial infarction. The patient had a baseline LDL-C of 2.28 mmol/L (88 mg/dL) and was not on a statin at baseline, and LDL-C 2 months prior to hospitalization was 3.1 mmol/L (120 mg/dL. As part of her corrective treatment, atorvastatin 80 mg was started.

In the long-term safety database (Pool 2), cardiovascular history was balanced between the treatment groups with approximately a third reporting hypertension, 12% reporting dyslipidemia, and 5% reporting coronary artery disease. Approximately 11% of patients reported taking a lipid modifying agent. Of patients receiving any dose of sarilumab, 28 events were adjudicated as MACE in 26 patients representing approximately 4482 patient-years exposure for a rate of 0.6 patients per 100 patient-years (MACE primary) and 0.5 patients per 100 patient-years (MACE narrow). According to the applicant, this rate is not elevated compared to rates cited from the population-based longitudinal cohort study performed in The Health Improvement Network of CV death, non-fatal MI, stroke in RA patients on DMARDs of 1.11 patients/100 patient-years.

DMEP Reviewer's Comment: The lack of a long-term placebo-control group to compare rates of MACE is a major limitation of the data's ability to inform sarilumab-associated CV risk. The use of an external control group's rate of cardiovascular events to contrast

with sarilumab is limited, since controlling for confounders to a sufficient degree to permit appropriate comparisons and reliable conclusions about the two groups may be impossible.

As shown in the table below when divided by initial dose, a numerically higher incidence and exposure-adjusted event rate for MACE primary and MACE narrow is observed in the sarilumab 200 mg Q2W group compared to the sarilumab 150 mg Q2W group.

Table 6. Number (%) of patients with adjudicated treatment-emergent MACE and number of events (per 100 patient-years) during the entire TEAE period – Sarilumab+DMARD long-term safety population (Pool 2)

	Sarilumab+DMARD					
CV Events Category	150 mg q2w Initial Dose (N=1155)	200 mg q2w Initial Dose (N=1351)	Any Dose (N=2887)	150 mg q2w Initial Dose (PY=701.9) n_E (n_E/100 PY)	200 mg q2w Initial Dose (PY=1758.6) n_E (n_E/100 PY)	Any Dose (PY=4481.8) n_E (n_E/100 PY)
MACE (primary)	2 (0.2%)	12 (0.9%)	26 (0.9%)	2 (0.3)	12 (0.7)	28 (0.6)
MACE (narrow)	2 (0.2%)	11 (0.8%)	23 (0.8%)	2 (0.3)	11 (0.6)	24 (0.5)
CV Death	1 (<0.1%)	3 (0.2%)	7 (0.2%)	1 (0.1)	3 (0.2)	7 (0.2)
Myocardial infarction	0	0	1 (<0.1%)	0	0	1 (0.0)
Other Cardiovascular Causes	1 (<0.1%)	2 (0.1%)	5 (0.2%)	1 (0.1)	2 (0.1)	5 (0.1)
Undetermined cause of death	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.1)	1 (0.0)
Myocardial infarction (non-fatal)	0	3 (0.2%)	10 (0.3%)	0	3 (0.2)	10 (0.2)
Hospitalization for unstable angina (non-fatal)	0	0	0	0	0	0
Stroke (non-fatal)	1 (<0.1%)	5 (0.4%)	7 (0.2%)	1 (0.1)	5 (0.3)	7 (0.2)
Hospitalization for transient ischemic attack (non-fatal)	0	1 (<0.1%)	3 (0.1%)	0	1 (0.1)	4 (0.1)

PY: Patient-years, CV: Cardiovascular, MACE: Major adverse cardiovascular events.
MACE (primary) includes CV Death, MI, Stroke, Hospitalization for unstable angina (UA) or Hospitalization for Transient Ischemic Attack (TIA).
MACE (narrow) includes CV Death, MI, or Stroke.
n (%) = number and percentage of patients with at least one adjudicated treatment-emergent CV event.
nE(nE /100 PY) = number of events and number of events per 100 patient-years.
PY for a treatment group is the total treatment duration of the treatment group.

Source: BLA 761037, ISS, Table 97

DMEP reviewer's comment: It is this reviewer's opinion that the number of MACE events and duration of exposure in the initial 150 mg Q2W group is too small to conclude the presence of a sarilumab dose-response for MACE events. Due to study design, it should be noted that there are only 6 (0.5%) patients in the 150 mg Q2W initial dose group with exposure greater than 96 weeks compared to 399 (29.5%) patients in the 200 mg Q2W group. Using patient-years of exposure may be misleading if the study does not have an adequate number of subjects studied for a sufficient duration to assess this risk, since it would be reasonable to expect that long-term exposure to the elevated lipid levels may be necessary to adversely impact the pathophysiology of atherosclerosis and its consequences.

Table 7. Exposure to Sarilumab – Long term safety population (Pool 2)

	Sarilumab+DMARD		
	150 mg q2w Initial Dose (N=1155)	200 mg q2w Initial Dose (N=1351)	Any Dose (N=2887)
Number of patients with duration of study treatment by category [n(%)]			
≥ 1 day	1155 (100%)	1351 (100%)	2887 (100%)
>12 weeks	995 (86.1%)	1117 (82.7%)	2556 (88.5%)
>24 weeks	560 (48.5%)	947 (70.1%)	2170 (75.2%)
>48 weeks	296 (25.6%)	701 (51.9%)	1546 (53.6%)
>96 weeks	6 (0.5%)	399 (29.5%)	1020 (35.3%)
>144 weeks	1 (<0.1%)	179 (13.2%)	624 (21.6%)
>192 weeks	0	6 (0.4%)	192 (6.7%)
>240 weeks	0	0	22 (0.8%)

Note: Patients are counted in a treatment group based on the treatment actually received.

Note: 150 mg q2w initial dose or 200 mg q2w initial dose is up to dose modification or end of the study; Any dose includes the exposure on all sarilumab doses: 100 mg qw, 100 mg q2w, 150 mg qw, 150 mg q2w, and 200 mg q2w.

Source: BLA 761037, ISS Table 15

Additional analyses

Model-based analyses were performed on endpoints for which additional information beyond what is conducted on placebo-controlled population (Pool 1) or sarilumab+DMARD population (Pool 2) may be of interest. All the safety data on either placebo or sarilumab from the intergrated sarilumab+DMARD studies were included in the analyses (ie, placebo exposure from Pool 1 and sarilumab exposure from Pool 2).

There were 1, 2, and 12 events on placebo, sarilumab 150 mg, and 200 mg, for incidence rates per 100 person-years of 0.3, 0.3, and 0.7, respectively. According to the applicant, this yielded rate ratios comparing 150 mg and placebo of 1.09 (95% CI: 0.10, 11.86) and comparing 200 mg and placebo of 2.68 (95% CI: 0.35, 20.76). The applicant also did one more analysis comparing placebo with an "Any Sarilumab" group that appears to have combined the 150 and 200 mg arms and also included events and follow-up time from the long-term open-label extension study. There were 27 patients with a MACE in this group, for an incidence rate of 0.6 per 100 person-years, and a rate ratio versus placebo of 2.38 (95% CI: 0.33, 17.11).

Project Code / Study Number / Analysis: SAR153191 / OVERALL / CSS

1.12 Other additional analyses

1.12.3 Model based analyses

1.12.3.6 Model based analyses on patients with at least one MACE (primary) during the entire TEAE period - Sarilumab+DMARD population including placebo (Pool 1 and Pool 2)

Treatment	Raw incidence rate n/N(%)	Exposure adjusted incidence rate n/PY (rate per 100PYs)[a]	Rate ratio vs. Placebo +DMARD (95% CI)	Rate ratio vs. Sarilumab 150mg q2w +DMARD (95% CI)
Placebo + DMARD doses	1/661 (0.2)	1/382.4 (0.3)		
Sarilumab 150mg q2w initial dose + DMARD	2/1155 (0.2)	2/701.7 (0.3)	1.09 (0.10 , 11.86)[b]	
Sarilumab 200mg q2w initial dose + DMARD	12/1351 (0.9)	12/1756.3 (0.7)	2.68 (0.35 , 20.76)[b]	2.45 (0.53 , 11.24)[b]
Any Sarilumab + DMARD doses	27/2887 (0.9)	27/4469.7 (0.6)	2.38 (0.33 , 17.11)[c]	

PY: Patient-years.

[a] Number of patients with at least one event per 100 patient-years, where the exposure time for patients who have experienced the specific adverse experience was defined as the time to first adverse experience of interest whereas the exposure time for those who have not had this adverse experience was total TEAE period duration.

[b] The between-treatment Exposure-adjusted rate difference and its 95% confidence interval were estimated using the GEE that adjusted for treatment, study, and the important baseline factors (ie, age, gender, weight, steroids use, and prior biologic use).

[c] The hazard ratio and its 95% confidence interval were estimated using the Cox proportional hazard model with repeated measures, adjusted for treatment, study, and the important baseline factors (ie, age, gender, weight, steroids use, and prior biologic use).

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Source: BLA 761037, ISS Appendix 1.12.3.6

DMEP Reviewer's Comment: We would defer to our colleagues with statistical expertise to opine on the validity of this model-based analysis. We would note that a MACE event in the placebo group is represented in this analysis.

VI. Recommendations

The following questions have been posed by DPARP to DMEP:

Questions:

Sarilumab is a fully human IgG1 mAb to IL-6R. As has been seen with other IL-6 inhibitors, an elevation in all lipid parameters (LDL, HDL, triglycerides) has been noted with sarilumab. Additionally, there is a suggestion of a possible dose response with more primary MACE events in the higher dose (200mg q2wk) treatment arm as compared to the lower dose (150mg q2wk) in the long term treatment population. Do you believe these lipid parameter changes are significant? Do you believe that they may be correlated with an increased risk of cardiovascular events? If so, do you feel that a post-marketing cardiovascular outcome trial would address this possible concern?

DMEP Response: Rheumatoid arthritis, a chronic autoimmune inflammatory joint disorder affecting more than 1.3 million Americans, is associated with greater risk of cardiovascular disease. A meta-analysis suggested patients with RA have a 50% higher risk of cardiovascular events and mortality compared to the general population.[4] The relationship between RA and increased CV disease is not fully explained by traditional assessments of cardiovascular risk (i.e. evaluating lipids and presence of various risk factors such as smoking, hypertension, family history, and diabetes). It has been hypothesized that the chronic pro-inflammatory state observed with RA is a primary contributor to cardiovascular pathology.[5] Recently, a Mendelian randomization analysis suggested a causal relationship between the IL-6 receptor pathway which mediates inflammatory responses initiated by the cytokine IL-6 and coronary heart disease.[6] Indeed, targeting inflammation to reduce cardiovascular risk is the recent focus of clinical trials.[7,8] Ongoing CV outcomes trials are testing the effects of an anti-inflammatory therapy on CV risk (e.g., the Novartis-sponsored CANTOS trial [NCT01327846], which is testing canakinumab, a human mAb against IL-1β).

Unlike the general population, where there is a linear correlation with LDL-C levels and cardiovascular risk, patients with RA, despite higher CV risk, tend to have lower total

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[4] Avina-Zubieta JA et al. Risk of cardiovascular mortality in patients in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690-7.
[5] Hannawi S et al. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. Arthritis Res. Ther 2007; 9(6):R116
[6] Hingorani AD et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomization analysis. Lancet 2012;379:1214-24.
[7] Everett BM et al. Rationale and design of the cardiovascular inflammation reduction trial: a test of the inflammatory hypothesis of atherothrombosis. Am Heart J. 2013;166:199-207.e15.
[8] Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. Circ Res. 2016;118:145-56.

cholesterol and LDL-C in the setting of active inflammation. This relationship has been described as a "lipid paradox".[9] Other disease conditions with inflammation have been associated with similar lipid changes and CV risk.[10] This complex interplay of inflammation with lipid levels and CV risk complicates conclusions about the clinical significance of the observed elevations in lipids with sarilumab, especially as they are occurring in tandem with reductions in the inflammatory biomarker, CRP. The net effect on CV risk of the anti-inflammatory mechanisms (if any) and the increases in atherogenic lipids such as LDL-C is unknown.

In general, of the lipid parameters, the evidence for LDL-C and risk for cardiovascular disease is the most robust. A meta-analysis of statin trials estimated that each 1.0 mmol/L (~40 mg/dL) reduction in LDL-C results in an approximate 22% reduction in major CV events.[11] In sarilumab placebo-controlled trials, relative to baseline, the mean change after 4 weeks of treatment with sarilumab every 2 weeks was approximately 16% (14 mg/dL in this population), compared to a 2% increase in the placebo group. In a head-to-head comparison, sarilumab-associated lipid elevations (LDL-C ~18% mean percent change from baseline) were similar to increases in lipids observed with tocilizumab (LDL-C ~21% mean percent change from baseline), a currently approved RA treatment with the same mechanism of IL-6 receptor blockade. It is not clear if this effect on lipids represents suppression of background inflammation, a specific effect on IL-6 receptor pathways, or an off-target effect of these drugs.

Other drugs are associated with dyslipidemia, including anti-hypertensives (thiazide diuretics [increase cholesterol and TG] and certain beta blockers [increase TG, decrease HDL-C]), immunosupressants (cyclosporine and tacrolimus), and protease inhibitors. Although cardiovascular outcome trials using thiazide diuretics (Systolic Hypertension in the Elderly Program) and beta blockers (Beta-blocker Heart Attack Trial) have demonstrated positive effects on cardiovascular endpoints, the degree of cardiovascular risk as a result of pharmacologically induced dyslipidemia is unpredictable and is most likely dependent on a multitude of factors including the disease condition, the drug's mechanism, and baseline traditional risk factors.[12, 13]

In theory, if the statin-based relationship between LDL-C and CV risk were to hold for drug-induced <u>increases</u> in LDL-C and could be extrapolated to the RA population, the magnitude of change could be on the order of 8% compared to placebo. However, this quantification of risk is speculative, especially considering that sarilumab induces

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[9] Myasoedova E et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann. Rheum. Dis. 2011; 70:482-87.
[10] Liu Y et al. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA 2004; 291(4): 451-9.
[11] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376:1670-81.
[12] Byington RP et al. Propanolol-induced lipid changes and their prognostic significance after a myocardial infarction: the beta-blocker heart attack trial experience. Am J Cardiol.1990;65(20):1287-91.
[13] Kannel WB et al. Long-term cardiovascular risk with protease inhibitors and management of the dyslipidemia. Am J Cardiol 2004;94:901-6.

favorable changes in inflammation, which may be a key contributor to CV risk in patients with RA. Furthermore, we note that sarilumab modestly increases HDL-C, which could be considered favorable since epidemiologic studies have observed an inverse relationship between HDL-C and CV risk, but pharmacologic interventions to increase HDL-C have not consistently predicted cardiovascular benefit; therefore, it is unknown if the observed changes in HDL-C with sarilumab would ultimately be positive.[14,15]

Similar uncertainty surrounds triglycerides. Although epidemiological evidence suggest elevated TG appears to be a risk factor for CVD, it is unknown whether drug-induced changes in TG will impact CV risk.[16] *However, severe elevations in TG levels (≥500 mg/dL) cause concern for a risk of acute pancreatitis. In the sarilumab development program, a total of 119 patients (4.1%) in the sarilumab+DMARD long-term safety population had a triglyceride value >495.6 mg/dL. None of these patients experienced pancreatitis, however (as determined by the search of SMQ acute pancreatitis by the applicant).*

Given the variable length of drug exposure and small number of events (total of 28 events adjudicated as MACE in 26 patients treated with any dose of sarilumab in long-term safety pool-Pool 2), this reviewer would consider any results generated regarding overall hazard ratios as preliminary and unstable.

If it is critical to characterize the effect of sarilumab on CV risk in order to determine whether the overall benefit/risk is favorable, a CVOT would be necessary. We note that few patients were taking lipid-modifying agents at baseline in this development program; it would be interesting to know whether concomitant use of LDL-C-lowering drugs (e.g., statins) mitigates the lipid abnormalities associated with sarilumab. If so, it is plausible that labeling could communicate that healthcare providers should follow lipid levels and treat accordingly; of course, this would assume that the changes observed in lipids mediate any sarilumab-induced increase in CV risk. Noting the precedent for requiring a CVOT to establish the CV safety of tocilizumab, however, it would appear that similar consideration would need to be given for sarilumab. It is our understanding that this requirement will be discussed more broadly within the Center in the near future.

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[14] AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. NEJM 2011;365:2255-67.
[15] Dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. NEJM 2012;367:2089-99.
[16] Rosenson RS et al. Genetics and causality of triglyceride-rich lipoproteins in atherosclerotic cardiovascular disease. JACC 2014;64:2525-40.

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/s/

MARY D ROBERTS
06/10/2016

JAMES P SMITH
06/13/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, Ophthalmic

Date: April 12, 2016

To: Christine Ford, Office of New Drugs, WO22-3306
christine.ford@fda.hhs.gov

Sandra Barnes, Office of New Drugs, WO22- 3312
sandra.barnes@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Christine Ford

Through: LT Viky Verna, Combination Product Branch Lead, Respiratory, ENT, General Hospital, Ophthalmic (REGO), DMQ, OC, CDRH, OMPT, WO66-3435

Viky Verna -S

Digitally signed by Viky Verna -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Viky Verna -S, 0.9.2342.19200300.100.1.1=2000495623
Date: 2016.04.14 20:52:55 -04'00'

From: Jamie Kamon-Brancazio, REGO, DMQ, OC, CDRH

Applicant: Sanofi-Aventis U.S. LLC
55 Corporate Drive
Bridgewater, New Jersey 08807
FEI# 3003596612

Application # BLA-761037

Consult # ICC1600148

Product Name: Sarilumab 150 and 200 mg prefilled syringes

Pre-Approval Inspection: No

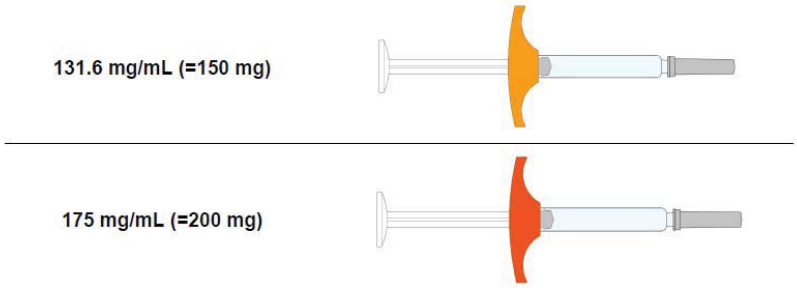
Documentation Review: Additional Information Required

Final Recommendation: **DELAY**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA-761037.

PRODUCT DESCRIPTION

(b) (4) indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs). The container closure system for sarilumab solution for injection is composed of the bulk prefilled syringe assembled with a plunger rod required to allow delivery of the PFS content and a finger flange to facilitate PFS grasping and handling.



REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Sanofi-Aventis U.S. LLC
   55 Corporate Drive
   Bridgewater, New Jersey 08807
   FEI# 3003596612

   Responsibility – Applicant

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on March 16-27 2015, comprised of drug coverage and was classified NAI.

Inspectional Recommendation:

An inspection is not required because:

- A recent inspection of the firm was acceptable.
- The firm does not perform manufacturing activities involving the the device constituent part. Therefore, the firm's compliance with 21 CFR Part 4 will be assured through the documentation review.

NOTE: As the applicant, the firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements.

2. Sanofi Winthrop Industrie

1051 Boulevard
Industriel
76580 LeTrait, France
FEI# 3003259844

Responsibility- Manufacture of bulk PFS and PFS, labeling and packaging the PFS, analytical release and stability testing, and post-approval stability studies

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on April 6-14 2015, comprised of drug coverage and was classified NAI.

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

3. Sanofi - Aventis U.S. LLC
   6244 Lemay Ferry Road
   Saint Louis, MO 63129
   FEI# 1000117606

   Responsibility – Secondary packaging and release for distribution of PFS.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection conducted on February 4-12, 2014 comprising of drug coverage and was classified NAI.

Inspection Recommendation:
An inspection is not required because:

- The firm's recent drug inspection was acceptable.

NOTE: The firm is responsible for activities related to the manufacturing and development of the final combination product, therefore the next inspection at the firm should cover compliance with applicable Quality System (QS – 21 CFR 820) requirements. (See Inspectional Guidance at the end).

DOCUMENTATION REVIEW
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20
Syringes are supplied sterile [redacted] (b) (4) and ready for use to Sanofi Winthrop Industrie (Le Trait). Syringe with staked needle and soft needle shield are controlled by the

supplier who delivers to Sanofi a certificate of conformity. The supplier is subject to regular audits as part of Sanofi Quality Assurance Program. Sanofi Winthrop Industrie performs all quality control testing of the syringes in addition to control of subcontractors. Sanofi has defined Quality Policies and Objectives. Sanofi has established the quality management system that comprises four elements, as described in the Quality Manual: Management Responsibility, Resource Management, Process Management and Measurement, Analysis and Improvement. The Quality manual is in place at Sanofi Winthrop Industrie, Le Trait. Sanofi's plan for quality is through the use of an integrated quality management system represented in the document hierarchy.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

Sanofi has procedures in place to control the design of the elements of the development activities and to ensure specified design requirements are met. The firm creates a Design Development Plan to describe all of the development and design activities, including planning, needs, and responsibilities. Design Input identifies user needs compiling information in reference to functional performance and design analysis to develop the design outputs. Design reviews are performed to assess the design result and are approved by Project Management and Quality.

Design verification activities are performed to document with objective evidences that the Design outputs meet the design input requirements, in order to evaluate and demonstrate conformance. For finished combination product, performance test are performed as part of the design verification program. Design validation activities are performed to document with objective evidences that the combination product complies with defined user needs and its intended use. Design Transfer activities ensure correct transfer of all documentation, methods, process and specifications to the industrial manufacturing site. Design changes are tracked into the DHF and managed according to a design change system to evaluate and control its implementation.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Sanofi has a purchased material management process and procedures in place which include:

- Evaluation and selection process for qualification of suppliers and materials

- Control over suppliers, including audits of the suppliers and sub-contractors

- Disposition of purchased materials

- Maintenance of associated quality records; acceptable suppliers

- Management policy for change notification and approval of changes in supplier or process components to determine whether such changes could affect the quality of the product.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100
The firm states, an internal SOP is in place at Sanofi Winthrop Industrie, Le Trait, which applies to all corrective/preventive actions resulting from:

- An investigation following an internal quality complaint or a deviation (including confirmed OOSs/OOTs),
- A laboratory anomaly (laboratory error),
- A return or batch recall,
- The analysis of a deviation recorded during a regulatory group or client inspection, self-inspection, or supplier and subcontractor audit,
- A trend analysis,
- An annual product or quality reviews,
- The implementation of a change with a measure of efficacy.

The firm did not provide a summary of analysis of sources of quality data to identify existing and potential cause of nonconforming practices and products; investigation of the cause of nonconformities, identification of actions needed to correct and prevent recurrence of non-conformances; and, verification or validation of the actions

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170
Installation is not required for this combination product.

Servicing, 21 CFR 820.200
Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls
The facility has been designed as a multi-product facility (b) (4)

Environmental controls are in place (b) (4)

As part of its quality assurance program, Sanofi Winthrop Industrie performs the appropriate qualifications in terms of major equipment and areas. Qualification is carried out by conducting installation, operational and performance qualifications, individually or combined.

Production Flow

The manufacturing process for production of sarilumab solution for injection in bulk PFS at Sanofi, LeTrait consists of the following steps:

(b) (4)

Acceptance Activities

Internal SOP's are in place at Sanofi Winthrop Industrie, Le Trait that define the rules and responsibilities for managing the specifications of raw materials and packaging, including any incoming inspection and testing to ensure acceptance/receipt of conforming materials and packaging according to the current regulation. Final acceptance tests are described to ensure combination products meet established specifications prior to distribution. Component acceptance criteria comply with AQL. Pre-filled syringes are released by visual inspection and the container closure integrity is tested using a dye ingress method.

Documentation Review Recommendation

This application was deficient overall. Additional information is required for an adequate documentation review.

Deficiencies to be conveyed to the applicant

The following deficiency have been identified while doing the documentation review of the application for Sarilumab 150 and 200 mg prefilled syringes, BLA-761037, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of non-conformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

RECOMMENDATION

The approvability of application BLA-761037, for Sarilumab 150 and 200 mg prefilled syringes should be delayed pending a response to the above listed deficiency:

(1) Additional information from the firm is needed to complete the documentation review.

Jamie Kamon-brancazio -S

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Date: 2016.04.15 07:22:06 -04'00'

Jamie Kamon-Brancazio

Prepared: JKamon-Brancazio: 04/12/16
Reviewed: VVerna: 04/14/2016

CTS No.: ICC1600148
BLA-761037

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Inspectional Guidance

Firm to be inspected:
Sanofi-Aventis U.S. LLC
55 Corporate Drive
Bridgewater, New Jersey 08807
FEI# 3003596612

CDRH recommends the inspection under the applicable Medical Device Regulations of Sanofi-Aventis U.S. LLC, located in Bridgewater, USA (FEI # 3003596612).

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact
Jamie Kamon-Brancazio
CSO,
REGO
DMQ
Office of Compliance, WO66 RM 3427
Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)
Francisco Vicenty
Chief
REGO
DMQ
Office of Compliance, WO66 RM 3426
Phone: 301-796- 2909

THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

Inspectional Guidance

Firm to be inspected:

Sanofi Winthrop Industrie
1051 Boulevard
Industriel
76580 LeTrait, France
FEI# 3003259844

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Phone: 301-796- 2909

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/s/

CHRISTINE H CHUNG

04/15/2016

uploading into darrts for CDRH-Office of Compliance review team
Christine Ford (formerly Chung)